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THE SIGNIFICANCE OF URINARY pH: CRITICAL OBSERVATIONS*

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It would appear to be unnecessary to discuss so simple a matter as urinary reaction but the average clinician not infrequently is puzzled by apparent inconsistencies and opinions which are expressed as fact. Although reaction can be interpreted as titratable acidity with or without additional data, present comments will be restricted almost entirely to reaction as measured by pH.

NORMAL URINARY REACTION

Henderson and Palmer¹ reported a normal range of urinary pH of 4.82 to 7.45 with a mean of 6.03. Later² a value of 8.7 was achieved after administration of excessive amounts of sodium bicarbonate and pH 4.7 was found to occur in the presence of a trace of free phosphoric acid. In collaboration with Newburgh³ they observed that normal subjects averaged pH 6; less than 1 per cent reached an acidity greater than pH 5.0 and less than 10 per cent pH 5.3 on 24-hour specimens. In 1914 Henderson and Palmer⁴ obtained an average of 5.98 on 222 cases, the normal being regarded as pH 6 ± 0.1 . Maslow,⁵ testing 24-hour specimens preserved with toluene, averaged pH 6.02 with a range of 5.1 to 6.8 on 141 adults.

Fischer⁶ citing Höber (1906) reported normal morning urine to vary from pH 5.3 to 5.5 (data calculated from cH) in 5 cases. Bowman and Pitts⁷ on catheterizing hospital patients without pyelitis observed a range of pH 4.6 to 7.6 on morning urine. Lloyd-Williams⁸ regarded pH 5.5 to 8.0 as the "symptomless zone" although he noted that pH 5 to 7 usually was the accepted normal range.

Marshall⁹ states that human urine probably never becomes more alkali-

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line than pH 8, this value being reached only under therapy. The maximum urinary concentration of sodium bicarbonate is about 0.22 molar and is supposedly not exceeded even when the body has occasion to rid itself of greater amounts of this base.¹⁰

In our experience, values on normal individuals fluctuate throughout the day about pH 6, the extreme limits of oscillation being 4.6 and 8.0. These values are given for room temperature. Correction to 38° C. necessitates subtraction of approximately 0.2 pH from observations made at 25° C.

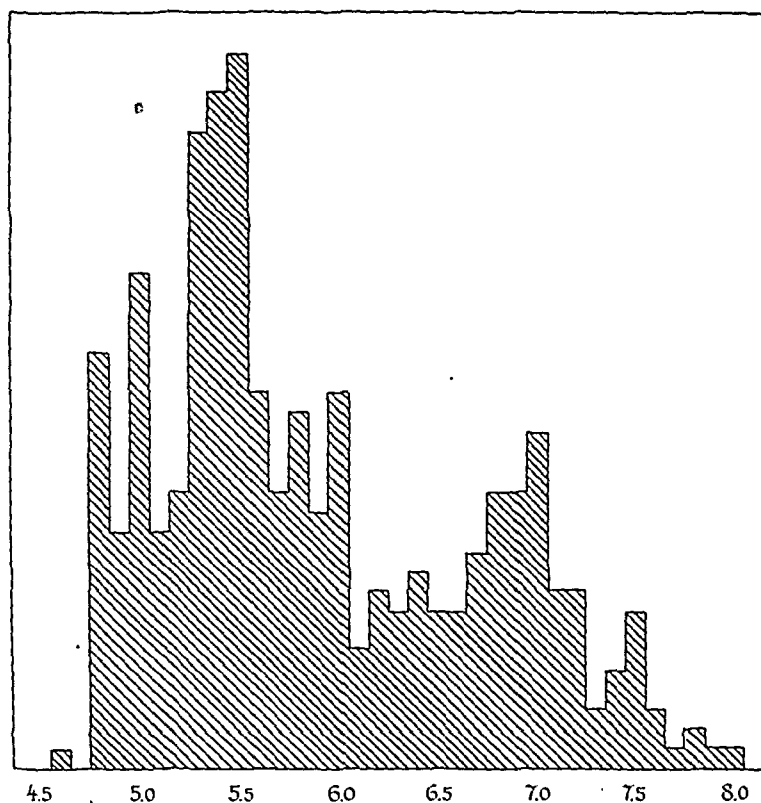


FIG. 1. Frequency distribution of 417 urine specimens on the same individual.

Figure 1 demonstrates the frequency distribution of 417 urine samples on a single individual. These were not specimens collected at random but represent every voiding for periods as extensive as two weeks at a time. Reactions below pH 6 account for 251 (60 per cent) of the specimens. Only 59 (11.7 per cent) reached pH 7 or higher. Although these observations include short intervals in which acidic-ash and alkaline-ash diets were followed, a mixed diet was the customary routine. The tests were conducted in summer when a plentiful variety of fresh fruits and vegetables was available. Although the protein intake was better than average, the amount of meat and fish consumed was moderate. These data were assembled under conditions which, from a nutritional standpoint, would be

considered wholly satisfactory. The tests were completed within 30 seconds of voiding, the subject serving as analyst.

The surprising degree of acidity noted might not be duplicated, however, under similar circumstances if the specimens were spaced further apart. In many instances very small volumes (5 to 30 ml.) were obtained for the specific purpose of ascertaining how rapidly the reaction might undergo change. In particular, the effect of ingesting food was studied and it was found that the *immediate* response to a meal was a change in the direction of greater acidity.¹¹ The reaction often varied by as much as two pH units in voidings less than 30 minutes apart.

From investigations reported elsewhere¹¹ it may be concluded that there is no single value for urinary pH which may be regarded as normal. Normality is characterized by variability. Furthermore, the daily fluctuations tend to form a pattern which is typical of the individual. These fluctuations constitute an acid-base tide the effect of which usually is manifest in the presence of incidental or experimental factors which also influence urinary reaction. In brief, it is not possible to correlate in any simple fashion the reaction of a single urine specimen with physiologic behavior or with experimental conditions.

PATHOLOGIC URINARY REACTION

If it is difficult to define any one value as the normal pH of urine, it is doubly so in pathologic states. Henderson and Palmer¹ reported pH 5.33 as the mean for "cardio-renal disease." These same investigators, together with Newburgh,³ observed in cardiac decompensation pH values of 4.7 to 5.3 (average 4.9) on 24-hour specimens. Höber (1906) cited by Fischer⁶ encountered in a few cases of nephritis morning urine of pH 4.6 to 5.3 (data calculated from cH), the greatest acidity being seen in the acute forms with diminished fluid output, much albumin and many casts. Ziegler and Brice¹² found that the majority of cases showed alkaline urine in fatal uremia.

Lloyd-Williams⁸ presents some very startling values for urinary pH, such as 3.3 and 3.8 in elderly persons whose only complaint apparently was "frequency of micturition and scalding." The same symptoms were reported in a child whose urine was pH 8.7, no sediment being present. This investigator states that "in febrile conditions a figure of 4.2 can easily be reached." These results are far beyond anything we have ever seen.

Fixation of Urinary Reaction. If definite variation of urinary reaction is the normal behavior, fixation is to be regarded with apprehension. Although "fixation of pH" may be sufficient for clinical purposes, these logarithmic values correspond to different grades of acidity with change in position on the pH scale and, therefore, cannot be readily compared. Even the term *average pH* may be somewhat absurd under strict interpretation. The authors have used a system which permits a numerical evaluation of

urinary variation in reaction by converting pH values into "acid activity" units.¹³ Preliminary observations have shown that the *difference* between the highest and lowest reading on a series of 8 to 10 urine specimens voided during 24 hours normally reaches 50 "acid activity" units or points. In our opinion, the extent and frequency of urinary change in reaction are a measure of renal efficiency. No method has been found which will "force" the excretion of highly acid urine for contrast with a strongly alkaline specimen within fixed time. In other words, it has been impossible either by administration of drugs or by dietary manipulation to shift the urine reaction deliberately from one extreme to the other.

In mild nephritis we have encountered differences of 20 to 30 "points" whereas in terminal nephritis the difference has been less than 1. A case of bacterial endocarditis (fatal) was characterized by extremely acid urine with variations from pH 4.7 to 5.0 which correspond to an "acid activity" difference of 100. Such observations, however, require confirmation from further clinical experience.

Anomalies of Urinary Reaction. The reaction of the urine is no dependable indication of the existence of acidosis or alkalosis. With *normal kidney function*, both the ingestion of acid-producing or acidifying drugs and the accumulation of ketonic acids due to metabolic disturbances will result in the excretion of unusual amounts of acid. After several days of excessive acid intake, however, the urinary pH will rise in spite of continued acid ingestion. Furthermore, ketonuria is not necessarily associated with acid urine. Ziegler and Brice¹² noted six alkaline specimens which contained a trace of acetone. They regarded this finding as rather unusual and not understood. Schrader¹⁵ is cited as having reported the same phenomenon. Such cases have been seen repeatedly in this laboratory.

Although not an every-day occurrence, it is not unusual for the "admission urine" of surgical patients to be neutral or alkaline in the presence of traces or small amounts of acetone. We have noted this particularly with cases scheduled for surgery involving the alimentary tract, as carcinoma of the mouth, appendectomy, perianal abscess, and hemorrhoids. These findings are such as might be expected since the apprehension which escorts many surgical patients to the hospital is not conducive to renal efficiency, the consequence being diminished excretion of acid.¹¹ Concurrently, the nutritional status of these patients is generally unsatisfactory, as reflected by the urinary ketones.

In loss of fluids through vomiting, ketogenesis ensues unless glucose in adequate amounts is introduced into the body. These ketones appear in the urine regardless of its reaction. Furthermore, the administration of large doses of sodium bicarbonate to normal persons experimentally or to others therapeutically so affects the oxidation of glucose that ketonic acids result from faulty combustion of the fats, in which case appreciable amounts of NaHCO_3 and ketones are excreted simultaneously. It should be stressed

that "acetone breath" and ketonuria are usually but not invariably associated with acidosis.

Acid Urine in Alkalosis. In preserving the *total* electrolyte content of plasma the kidneys ordinarily distinguish between sodium and potassium, chloride and bicarbonate, but they will allow the normal ratios of these radicals to undergo drastic alteration if the total base is low. When this occurs, the kidneys will not excrete bicarbonate although definite alkalosis (relative excess of plasma sodium bicarbonate) exists. Likewise, no alkaline urine results from overventilation if the body can ill afford to throw away base. Also, prompt excretion of ingested water does not occur since its removal entails loss of at least some base.

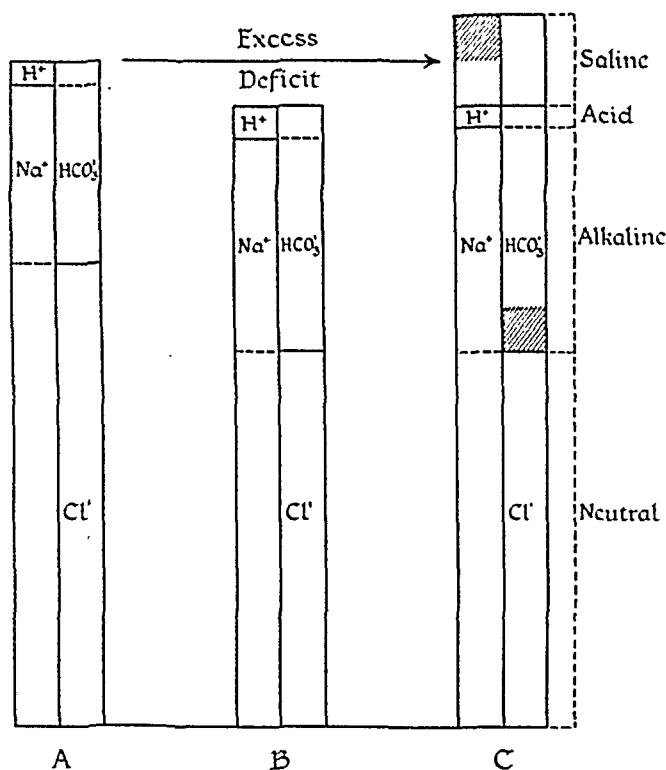


FIG. 2. Diagrammatic representation of the relationship between the chief electrolytes of the plasma.

In the blood plasma, Na⁺ is balanced by varying amounts of HCO₃⁻ and Cl⁻. As is well known, the NaHCO₃ is alkaline in reaction whereas the NaCl is neutral. A small amount of H⁺ is balanced by HCO₃⁻ and is, of course, acid. For ease in representation, figure 2 has not been made proportional to the actual normal ratios (Cl:HCO₃: : 4:1, and NaHCO₃:H₂CO₃: : 20:1, both suitably expressed). In pyloric obstruction, for instance, there is greater loss of Cl⁻ than Na⁺, together with marked dehydration. The consequence is a drop in the total Na⁺ in the plasma but a relative increase in the bicarbonate which replaces part of the lost chloride—a base

deficit with increased alkalinity (figure 2B). Were the kidneys to excrete some of the NaHCO_3 to restore the ratio of bicarbonate to chloride, the sodium would be reduced to an intolerable level. Despite the presence of alkalosis, such urine as is excreted is acid, first because it allows greater concentration of waste products¹² and second, because it conserves body base. When, however, saline is administered, both water and base become available. Sodium is excreted until the electrolyte level is normal; it carries with it the unwanted HCO_3^- , thus producing an alkaline (or at least less acid) urine (figure 2C).

Nicol¹⁶ has pointed out that the kidneys quickly compensate for alkalemia unaccompanied by dehydration, but severe vomiting followed by dehydration results in a toxic nephritis as evidenced by albuminuria and the appearance of casts and red blood cells in the urinary sediment, the urine remaining acid despite the alkalemia. Nicol observed that correction of the dehydration with sodium chloride brought about the disappearance of the albumin, cells and casts and the excretion of an alkaline urine so long as the plasma CO_2 C.P. remained elevated. It was concluded that dehydration results in oliguria which produces tubular damage (as shown by postmortem findings) so hampering the excretion of alkali.

Unsuspected cases of alkalosis have been encountered among both diabetics and nephritics. One such, a patient with diabetes, arteriosclerosis and chronic myocarditis was admitted for treatment of a carbuncle. Analysis of the blood showed: sugar 288 mg. per cent, CO_2 C.P. 75.8 volumes per cent, and pH 7.6. The urine was acid and contained 0.28 per cent sugar as well as two plus acetone and diacetic acid. At the time there was no explanation for the alkalosis.

Way and Muntwyler¹⁷ reported cases of renal disease showing relatively little nitrogen retention but marked elevation of blood pressure. Both pH and CO_2 C.P. were increased and chlorides lowered. Despite the blood alkalinity, the urine remained acid, often strongly so. With progression of the renal disability, acidosis ensued.

Myers and Booher¹⁸ reported two cases where strongly acid urine was noted in the presence of alkalosis due to administration of sodium bicarbonate. Issue was taken with Palmer¹⁹ who contended that sufficient check on the therapeutic use of this drug was obtained by testing the urine until it reached pH 7, at which time the bicarbonate was to be discontinued. Myers did not believe that the urine reaction was a safe guide since some individuals with apparently normal kidneys fail to excrete alkali readily. This belief has been borne out by repeated observations in this same laboratory; unfortunately, they have not been committed to the literature.

Alkaline Urine in Nephritic Acidosis. With progressive failure in renal function, elaboration of a concentrated acid urine becomes impossible. The fixation of pH at lower levels, which is seen in earlier nephritis, gradually shifts in the direction of neutrality. Death often ensues when the pH level reaches 6.5 to 6.8, the turning point of litmus. Where routine

urine is tested with litmus paper, it is reported as alkaline while still below pH 7. Added to this that urine of low specific gravity contains few buffer substances and readily changes its reaction to definite alkalinity on standing, it can be seen that the urine will frequently be "alkaline" despite the fact that these patients are acidotic.

Experimentally, Stieglitz²⁰ has observed that the secretion of an alkaline urine leaves the tubular cells acid, whereas increasing alkalinity of the cells results when acid urine is secreted. In nephritis this reciprocal relationship is altered, the injured cells remaining acid and the urine likewise. This does not necessarily imply, however, that the urine is strongly acid in all stages of nephritis as is commonly supposed.

ALTERATION OF URINARY REACTION

The urine reaction is amenable to change under certain conditions. No intelligent procedure can be outlined for specific application without a knowledge of the characteristics of the individual's acid-base curve.¹¹ Attack then can be directed against those points where the reaction is other than that desired, just as is done in apportioning the insulin dosage of the diabetic. For example, a daily curve which shows an "alkaline" specimen late in the forenoon with definite acidity holding throughout the remainder of the day can be flattened by selection of suitable foods or drugs a few hours earlier. Such a subject, however, would be difficult to alkalinize except with large doses of sodium bicarbonate. Similarly, a person whose only acid specimen was obtained on arising would resist fixation of the urine at pH 5. Alkalinization of this morning urine could be achieved only by medication at night, the wisdom of such a procedure being questionable.

Factors Affecting Urinary Reaction. In actual practice it will be found that the response of patients to acidification or alkalinization measures is highly variable and conditioned by manifold factors including such intangible ones as emotional states. Summarizing our experience with considerable hesitation, the primary tendency of various individual factors which influence urinary pH appears to be as follows:

Personality: In sthenic types, there is greater acidity, greater variability, and fixation is less readily achieved.

Water Excretion: Unless counteracted by other forces, increase in water output raises the pH. Water retention at night usually is associated with increased acidity. Loss of water through vomiting, diarrhea, catharsis, and sweating increases urinary acidity.

Emotional Status: Polyuria of nervous origin is associated with increased pH. Tense attitudes which diminish water excretion increase acidity. Apprehension may diminish the output of acid. Petty annoyance is apt to raise the pH. Working under pressure may lead to fixation at alkaline or acid levels despite diuresis. Sthenic individuals under pleasurable emotional stimulus tend toward greater acidity.

Meals: Ingestion of food more often than not is associated with immediate increase in acidity followed by changes dependent upon the composition of the food and related to the time of day.

Rate of Ventilation: Overventilation leads to diminished acidity if water and base are available for excretion.

Exercise: Diminished water output occurs together with increased acidity.

Fatigue: Where mental processes are involved, the pH rises.

Pathologic States: Edema formation is associated with greater acidity, discharge of edema with rising pH. Diabetic acidosis generally is accompanied by marked acidity unless ammonia excretion is high. There is fixation of urinary pH at unusually low levels in cardio-renal disease. In terminal nephritis neutrality is encountered. Those anomalies associated with loss of fluid through the alimentary tract have been discussed elsewhere at some length.

The observed urinary pH is always the resultant of several factors operating at one and the same time. These generalizations, then, will be helpful only as they are correlated and checked by the experience of others.

Means of Changing Urinary Reaction. The extent of urinary pH change desired, naturally, affects the selection of method for its alteration. There are many instances in the practice of medicine where general indisposition or specific complaints can be met with an altered dietary regimen. Those with a predilection for alkaline-ash foods will derive benefit from acid-producing foods, and vice versa. When changes in reaction are contemplated, it should be remembered that forcing fluids tends to raise the urinary pH while withholding water lowers it.

The ketogenic diet is not well tolerated by the majority who require definite acidification. The use of acidic-ash foods is more effective in the long run. As ordinarily applied, such a diet not infrequently fails to lower the urinary pH below 5.5. This is due not only to the characteristics of the individual's natural pH curve, but also to lack of strictness in arranging the diet. The absence of salad and cooked greens in particular may be annoying to the patient. These greens may be allowed once daily if ample amounts of cranberry, plum or prune juices are taken to the exclusion of other fluids. Where it is deemed advisable, lactic acid milk may be employed in lieu of the fruit juices suggested. Ice cream is permissible on both acidic and alkaline-ash diets.

Crance and Maloney²¹ in a preliminary report advised a regular diet acidified with 10-minim doses of concentrated nitrohydrochloric acid (18 parts HNO₃ to 82 parts HCl) after meals and late at night. At least one glass of water is taken with each dose. The use of hydrochloric acid, either alone or in conjunction with nitric acid, has been ineffective in lowering the pH to the neighborhood of 5 in our experience¹¹ whereas the benzoic and quinic acid fruits have easily accomplished this. It seems paradoxical, but it can be verified in practice, that withdrawal of hydrochloric acid medication

is followed by increase in urinary acidity, the diet remaining unaltered. This is occasioned by the fact that the elimination of water taken with the acid nullifies its effect inasmuch as the increased urinary volume results in an upward trend in the pH. Could the nitrohydrochloric acid be administered with less water it would be more effective.

The more common drugs for acidifying urine include sodium acid phosphate (average dose 10 to 30 gr.), sodium benzoate (average dose 15 to 30 gr.), ammonium chloride (average dose 15 gr., in amounts up to 120 gr. daily) and ammonium nitrate (dosage as for ammonium chloride). Ammonium or monoethanolamine mandelate (10 to 15 gr. in amounts up to 180 gr. daily) is employed for acidification and for its bactericidal effect. When used in conjunction with ammonium chloride, 10 gr. of the former and 7 gr. of the latter are usually given t.i.d.

On alkaline-ash diets the withdrawal of cereal products may constitute a hardship in which case two slices of bread daily may be allowed. Unless contra-indicated, an egg should be included every day except where the diet is of short duration. The melons, bananas, pears and apples are particularly well suited to raising urinary pH.¹¹ In preliminary experiments Shohl's citrate solution²² has proved to be useful where it has been impractical to alter the basic diet. This consists of 20 ml. of molar citric acid (210 gm. $\text{H}_3\text{C}_6\text{H}_5\text{O}_7 \cdot \text{H}_2\text{O}$ per liter) plus 30 ml. of molar citrate (294 gm. $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ per liter). Although the pH of the mixture is not unduly acid, the citrate is so concentrated as to require dilution of 5 to 10 times for ingestion. Milk can be used as a vehicle although water is usually more convenient. As dictated by the natural acid-base rhythm of the patient and the response to the citrate, the dose is administered as a whole or divided. In accordance with individual preference it can be taken before, after or during meals.

The use of this citrate can be illustrated with a case that showed pH 6.4, 6.8, 6.5, 7.1 and 7.0 during the period from 11:30 a.m. (when 50 ml. of citrate were taken) to 10:45 p.m. The same patient on the same basic mixed diet with the exception that cranberry juice was taken over the same time interval presented a lowering of urinary pH to 5.8, 5.6, 6.2, 5.9 and 5.5. This patient was not particularly prompt in the removal of either base or acid. A demonstrably normal subject reached pH 7.6 two hours after ingesting the citrate. Five hours later, despite the excretion of only 150 ml. in this interval, the urinary pH was 7.2. Cranberry juice (125 ml. with an equal amount of water) produced a pH of 5.0 and 5.3 respectively on precisely the same water output (360 ml.).

McClellan and Goldstein²³ compared urinary pH after the ingestion of plain and mineral waters which contained 2 to 5 gm. of the bicarbonate and carbonates of sodium, calcium, and magnesium per liter. When 500 or 1,000 ml. of mineral water were included with breakfast, the subsequent urinary reaction varied between pH 6.5 and 8.0 throughout the 24 hours. The greater the diuresis the more nearly the pH approached 7. The shift

into the alkaline range was directly proportional to the alkaline content of the different mineral waters used. To maintain continuously alkaline urine, 45 gm. of sodium bicarbonate may be required daily.²⁴

Reasons for Changing Urinary Reaction. To quote from Mason and Hellbaum²⁵: "Many physicians make a routine practice of prescribing alkalies, and also alkali diet, in the treatment of nephritis. They usually do so with no better reason than 'if it does not benefit the patient, it can at least do no harm.' Also the general public has been 'sold' on the idea that all human ills result from a 'too acid' condition, and the panacea is alkali. Berger and Binger²⁶ have observed impaired renal function accompanying alkalosis, resulting from the alkaline treatment of peptic ulcer. Steele²⁷ has also observed that renal damage may occur in the alkaline ulcer treatment before clinical symptoms of alkalosis appear. . . . Ziegler and Brice¹² warned against the indiscriminate use of alkalies, as alkalization of the urine may defeat the purpose, which is elimination of solids."

On the other hand,²⁵ "we have no evidence that prolonged use of an acid salt has an injurious effect on the kidney. Very recently Noth has reported the treatment of a case of Pick's disease in which 6 grams of ammonium nitrate were administered daily for over three years with no evidence of hepatic or renal damage."

Ziegler and Brice¹² found the acid type of therapy superior to the alkaline in managing nephritis. Mason and Hellbaum,²⁵ as well as others, have discovered that Lashmet's²⁸ treatment of nephritic edema "works." Essentially it consists of a low-protein, salt-poor, neutral-ash diet in conjunction with acid-producing salts and "forced" fluids.

The influence of alkalies on renal function has received considerable attention from various investigators. The weight of opinion is against promiscuous use of alkaline therapy because of the tendency toward renal damage. As already pointed out¹⁸ some persons with apparently normal kidneys do not eliminate alkali readily. Hardt and Rivers²⁹ were the first to describe toxic manifestations following alkaline treatment of duodenal ulcer where renal damage antedated the therapy and also where no such prior impairment existed. Shattuck, Rohdenburg, and Booher³⁰ also cited cases but noted that only a small group of ulcer patients receiving alkaline treatment were so affected.

In a short experimental study involving the use of calcium carbonate and magnesium oxide, McGee et al.³¹ believed that they had evidence of a slight depression of renal function. Berger and Binger²⁶ presented an exceptional case with duodenal ulcer that for years "consumed pounds of both calcium carbonate and sodium bicarbonate every week" without apparent impairment of renal function.

It is believed that alkalization should be attempted only with definite justification. Where extreme acidity is accompanied by frequency of micturition and a burning sensation, relief may be expected by inducing reac-

tions close to neutrality. There is no merit in achieving a continuously alkaline urine. It is of no benefit to the kidneys—rather the reverse. Since alkalization of urine causes increasing renal cellular acidity as demonstrated by Stieglitz,²⁹ there is indeed no justification for producing this abnormal state. Later³² applying experimental observations to the clinical paradox that diuresis may follow either alkali or acid therapy, Stieglitz suggested that the reversal of intracellular reaction produces physiologic irritation and thus renal diuresis by insult attributable to alkali whereas diuresis associated with the use of acids in nephritis probably results from some measure of physiologic neutralization of the renal secreting cells, thus improving their functional efficiency. Stieglitz has also shown that alkalization of nephritic animals does not reverse the acid reaction of the injured kidney cells.

There arise occasions, however, when alkaline urine may be desirable. Hemoglobinuria subsequent to transfusion has been found by McGowin et al.³³ to be associated with renal impairment in dogs due to blockage of the tubular lumen with masses of pigment although the transfused blood was compatible. Partial or complete urine suppression occurred on acidic diets, but so long as the urine was alkaline intravenous injection of large amounts of dog hemoglobin appeared to be innocuous.

An acidic diet is dehydrating whereas marked and sudden gain in weight follows the administration of sodium bicarbonate.²⁵ Not only in edema but also in epilepsy and in obesity may advantage of this fact be taken. Subcaloric diets do not always lead to the expected loss in weight. Prompt elimination of water and consequent weight reduction are encountered with acid formation and a low salt intake.

Pitfalls in Urinary Fixation. It is one thing to alter the composition of urine so as to increase or decrease the excretion of acid or basic substances; it is quite another matter to attempt to hold the pH at a predetermined level. Apart from persistent ammoniacal fermentation in the bladder or the administration of large amounts of suitable drugs, it is impossible to secure consistently alkaline urine. Although acidification is more readily achieved than alkalization, the initial low pH cannot be maintained indefinitely since metabolic adjustment is made for the increased ingestion of acidic substances if this is persisted in long enough to set in operation compensatory manufacture of ammonia. When the pH rises coincident with an increased output of ammonia regardless of the diet or further administration of acidifying drugs, the acid therapy should cease. Unless specifically contraindicated, a rational schedule calls for five days' acidification followed by two days of dietary relaxation in which the erstwhile forbidden foods and fluids are freely ingested. In particular, it is recommended that the Shohl citrate solution, previously mentioned, be employed in conjunction with a quart of milk daily.

On any acidification regimen, provision should be made for adequate intake of calcium. When cheese is tolerated, this item is invaluable. It

should be remembered that the rennet cheeses are ten times richer in calcium than those produced by acid coagulation. Since the acidic-ash diet is notably deficient in vitamin C, administration of ascorbic acid (50 mg. daily) is advised.

Continued acidification results in the loss of considerable calcium from the body. *Other circumstances permitting*, urinary calculi might be formed, in particular those composed of calcium oxalate. It is highly improbable that calculosis can be induced by altering the reaction of the urine, but prolonged fixation of pH might provoke crystallization under conditions conducive to stone formation. During acidification, therefore, the quantity and type of urinary deposit should be determined. The occurrence of a lateritious deposit should be viewed with apprehension and steps taken to decrease the need for the excretion of much uric acid.

It has been observed that urine as it leaves the ureteric orifices is already turbid in many vegetarians. It is recognized, of course, that ample supplies of cereals in the diet tend to off-set the alkalinity of vegetables and fruits. Neutral and alkaline urines, however, do not regularly exhibit the clarity of acid specimens but frequently show a copious deposit of phosphates. This turbidity, as a general occurrence, is most undesirable.

SUMMARY

1. Normality of urine reaction is characterized by variability within the range of pH 4.6 to 8.0, lower values being observed much more frequently than higher ones.

2. Abnormality of urine reaction is characterized by fixation at levels typical of the disease.

3. Alkalosis (relative excess of plasma sodium bicarbonate) in conjunction with base deficit is associated with acid urine. The administration of adequate amounts of saline is followed by excretion of "alkaline" urine.

4. "Acetone breath" and ketonuria are usually associated with acidosis but will also occur in conditions covered by the term "alkalosis." Ketones may be found in abnormal amounts in urine of any reaction.

5. Elevated plasma pH and CO₂ C.P. together with acid urine may be encountered both in diabetes and renal disease.

6. The reaction of the urine is not a safe guide in the avoidance of alkalosis due to sodium bicarbonate therapy.

7. The acidosis of terminal nephritis is accompanied by urine close to neutrality in reaction, the blood and urine pH values moving toward each other.

8. The acid-base ratios of the tissues, blood and urine do not rise and fall concomitantly. The former possess compensating mechanisms in which the kidneys play an important rôle. Adjustment so secured of necessity requires the formation of urine of markedly different reaction from that within the body. Urinary pH per se, therefore, is of limited significance.

9. The response of patients to acidification or alkalization is highly variable and conditioned by manifold factors including such intangible ones as emotional states. Some of these factors are mentioned.

10. The means of changing urine reaction and the reasons therefor are discussed.

11. The pitfalls encountered in acidifying or alkalizing measures are cited.

12. Any arbitrary attempt to fix or shift urinary reaction in the direction of greater alkalinity should be regarded in the same light as alteration of gastric acidity—a matter undertaken only by the competent physician on cases presenting definite pathology and achieved by means which do not ignore the body's other needs. The daily removal of the acid end-products of metabolism is not a thing to be deplored and the urine promptly alkalized. In so doing, the very purpose of urine formation may be defeated.¹²

BIBLIOGRAPHY

1. HENDERSON, L. J., and PALMER, W. W.: Intensity of urinary acidity, *Jr. Biol. Chem.*, 1913, xiii, 393.
2. HENDERSON, L. J., and PALMER, W. W.: On the extremes of variation of the concentration of ionized hydrogen in human urine, *Jr. Biol. Chem.*, 1913, xiv, 81.
3. NEWBURGH, L. H., PALMER, W. W., and HENDERSON, L. J.: Hydrogen-ion concentration of the urine in heart disease, *Arch. Int. Med.*, 1913, xii, 146.
4. HENDERSON, L. J., and PALMER, W. W.: On the several factors of acid excretion, *Jr. Biol. Chem.*, 1914, xvii, 305.
5. MASLOW, L. A.: Urinary pH and crystallography, *Jr. Urol.*, 1936, xxxv, 674.
6. FISCHER, M. H.: Edema and nephritis, 2d edition, 1915, John Wiley and Sons, New York.
7. BOWMAN, R. D., and PITTS, H. C.: Calcium and phosphatase studies in cancer of female sex with consideration of basal metabolic rate and urine pH, *Am. Jr. Obst. and Gynec.*, 1936, xxxii, 957.
8. LLOYD-WILLIAMS, I. H.: Musings on urinary pH values, *Jr. Roy. Army Med. Corps*, 1939, lxxii, 123.
9. MARSHALL, E. K.: The effect of loss of carbon dioxide on the hydrogen-ion concentration of urine, *Jr. Biol. Chem.*, 1922, li, 3.
10. DAVIES, H. W., HALDANE, J. B. S., and KENNAWAY, E. L.: Experiments on regulation of the blood's alkalinity, *Jr. Physiol.*, 1920, liv, 32.
11. BRIDGES, M. A., and MATTICE, M. R.: Control of urine reaction, *Am. Jr. Med. Sci.*, 1940, cc, 84.
12. ZIEGLER, E. E., and BRICE, A. T.: Reaction and specific gravity of the urine in relation to nephritis (a study of ten thousand urinalyses), *ANN. INT. MED.*, 1937, xi, 768.
13. BRIDGES, M. A., and MATTICE, M. R.: Over two thousand estimations of the pH of representative foods, *Am. Jr. Digest. Dis.*, 1939, vi, 440.
14. BRIDGES, M. A., and MATTICE, M. R.: Unpublished observations.
15. SCHRADER, J. C.: Alkalosis, *Jr. Iowa State Med. Soc.*, 1929, xix, 179.
16. NICOL, B. M.: Renal changes in alkalosis, *Quart. Jr. Med.*, 1940, ix, 91.
17. WAY, C. T., and MUNTWYLER, E.: Alkalosis, a clinical problem, *ANN. INT. MED.*, 1935, viii, 818.
18. MYERS, V. C., and BOOHER, L. E.: Observations on the excretion of an acid urine in alkalosis, *Proc. Soc. Exper. Biol. and Med.*, 1925, xxii, 512.
19. PALMER, W. W., SALVESEN, H., and JACKSON, H., JR.: Relationship between the plasma bicarbonate and urinary acidity following the administration of sodium bicarbonate, *Jr. Biol. Chem.*, 1920, xlv, 101.

20. STIEGLITZ, E. J.: Histologic hydrogen-ion studies of the kidneys, *Arch. Int. Med.*, 1924, xxxiii, 483.
21. CRANCE, A. M., and MALONEY, T. W.: A new acid medication in the treatment of bacilluria, *Jr. Urol.*, 1935, xxxiii, 657.
22. SHOHL, A. T., and BUTLER, A. M.: Citrates in the treatment of infantile rickets, *New England Jr. Med.*, 1939, ccxx, 515.
23. McCLELLAN, W. S., and GOLDSTEIN, R.: The pH of the urine as influenced by the ingestion of alkaline mineral waters, *Jr. Clin. Invest. (Proc.)*, 1938, xvii, 516.
24. BEST, C. H., and TAYLOR, N. B.: *The physiological basis of medical practice*, 1937, Wm. Wood and Co., Baltimore.
25. MASON, E. C., and HELLBAUM, A. A.: Acid-base water balance, *ANN. INT. MED.*, 1938, xi, 2206.
26. BERGER, E. H., and BINGER, M. W.: The status of the kidneys in alkalosis, *Jr. Am. Med. Assoc.*, 1935, civ, 1383.
27. STEELE, J. M.: Renal insufficiency developing during prolonged use of alkalis, *Jr. Am. Med. Assoc.*, 1936, cvi, 2049.
28. LASHMET, F. H.: The treatment of nephritic edema by acid, *Jr. Am. Med. Assoc.*, 1931, xcvii, 918.
29. HARDT, L. L., and RIVERS, A. B.: Toxic manifestations following the alkaline treatment of peptic ulcer, *Arch. Int. Med.*, 1923, xxxi, 171.
30. SHATTUCK, H. F., ROHDENBURG, E. L., and BOOHER, L. E.: Antacids in medical management of peptic ulcer, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 200.
31. McGEE, L. C., MARTIN, J. E., LEVY, F., and PURDUM, R. B.: The influence of alkalis on renal function, *Am. Jr. Digest. Dis.*, 1939, vi, 186.
32. STIEGLITZ, E. J.: Alkalis and renal injury, *Arch. Int. Med.*, 1928, xli, 10.
33. McGOWIN, E. L. OSTERHAGEN, H. F., and ANDERSCH, M.: Effect upon renal insufficiency from transfusion, *Arch. Int. Med.*, 1937, lix, 432.

TREATMENT OF STAPHYLOCOCCAL SEPTICEMIA WITH SULFAMETHYLTHIAZOLE AND SULFATHIAZOLE; A REPORT OF TWELVE CASES *

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THE reported mortality from staphylococcal septicemia associated with foci of all sorts varies from 8 to 90 per cent.¹⁻¹¹ Inspection of the summary of recent reports in table 1 shows that though reduction in the general mortality has followed the use of one or another therapeutic agent, the invasion of the blood stream by staphylococci is still a grave matter. Moreover, strict criteria for diagnosis are not always defined. Stookey and Scarpellino³ insisted upon the presence of three positive blood cultures for inclusion of cases in their series, and excluded all cases of osteomyelitis, but most authors have not laid down such rigid criteria. The presence of two positive blood cultures would seem to be a fair criterion in cases that are to constitute the basis of therapeutic evaluation, but in general, waiting for three positive cultures before beginning treatment is hardly justified.

Another gap in the armamentarium of evaluation is the lack of extensive data dealing with the mortality in bacteremic osteomyelitis. Stookey, Scarpellino, and Weaver¹¹ state, "Let it be recalled that in every case osteomyelitis is at its inception a bacteremia. The blood in a majority of cases eventually sterilizes itself, with the localization of the invading bacteria in certain bones." Robertson¹² said in 1938, "Some years ago, in studying cases of staphylococcal osteomyelitis, a routine examination of the blood for its bacterial count was made. If the culture was made a number of times, organisms were grown in every case." However, this statement is supported by neither a reference to the earlier work, nor by analytical statistical data. Despite these views, Baker and Shands¹ found that 70 per cent of 30 patients with bacteremic osteomyelitis died. It is generally agreed that osteomyelitis probably begins by transport of organisms to bone via the blood. May it not be, however, that the finding of bacteremia a week or more after the onset of symptoms represents a less favorable immunological situation, and accordingly a poorer prognosis than when the bacteria are recovered from the blood in the very beginning of the disease?

The evaluation of therapy in staphylococcal septicemia in general is more difficult than in pneumonia, for example, where case material is abundant, and alternate case studies can be made. Nevertheless, valuable data may accumulate by pooling reports from various clinics whose criteria

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From The Department of Internal Medicine, University of Cincinnati College of Medicine, and The Cincinnati General Hospital. This study was aided by two grants made in honor of Craig Yeiser.

of diagnosis are similar. It is the purpose of this communication to report our experience in the Cincinnati General Hospital with 27 cases of staphylococcal septicemia during the period 1933-39, and add 12 cases treated within the past year with thiazole derivatives of sulfanilamide.* Except as specifically indicated, all patients had at least two positive blood cultures. Our series includes all cases of staphylococcal septicemia, regardless of focus.

During the past year we have observed 12 patients treated with thiazole derivatives of sulfanilamide of whom eight have recovered. The four fatalities all occurred in patients with acute staphylococcal endocarditis. The distribution of the foci in the 12 cases was as follows: osteomyelitis, 3, of whom one had meningitis in addition; carbuncle, 2; gluteal abscess, 1; pyarthrosis, 1; fracture, 1; and endocarditis, 4.

REVIEW OF PREVIOUS CASES OF STAPHYLOCOCCAL SEPSIS AT THE CINCINNATI GENERAL HOSPITAL

In the files of the Cincinnati General Hospital from 1933 to 1939 are the records of 27 patients whose blood-streams were invaded by the staphylococcus. Of this group, 20 had at least two positive blood cultures. Of the seven patients with only one positive culture, three died within 24 hours of admission to the hospital, and two patients had but one culture made. The other two patients with only one positive culture survived. There were but four recoveries in the entire group, a gross mortality of 85.2 per cent.

The fulminating character of staphylococcus septicemias has been recognized for a long time, and is borne out by the present series. The average total illness in the fatal cases was 17 days, with extremes of 4 and 81 days. The average duration of illness before admission to the hospital was 8 days; that of the four recovered cases, approximately 14 days.

Nine cases were associated with infections of the skin, of which six occurred in the face or neck; all succumbed. One fatal case began as an infection of the prostate, and one of a pilonidal cyst. One patient had acute bacterial endocarditis, but the portal of entry in this case was not determined. Two septicemias secondary to uterine infection were fatal. Four of seven patients with osteomyelitis died. Five other foci were either uncertain or entirely obscure; one of these patients recovered. The mortality in the seven cases of osteomyelitis was 57.1 per cent; in the 20 other cases the mortality was 95 per cent.

Careful study of the isolated organisms was not made. Four strains were designated as *Staphylococcus albus*. Six were identified as hemolytic *Staphylococcus aureus*, and 12 merely as *Staphylococcus aureus*. Colony counts were reported in eight instances. In two cases there were fewer than 25 colonies; in two cases there were from 25 to 100 colonies; and in four there were 100 or more colonies per cubic centimeter.

* The drugs used in this study were generously supplied by the Winthrop Chemical Company, E. R. Squibb & Sons, and The Lederle Laboratories, Inc.

* During the period reviewed, treatment of several kinds was uniformly ineffective. Most of the patients received one or more blood transfusions and some received as many as twenty. Among the fatal cases, six patients received adequate doses of sulfanilamide and three of sulfapyridine; two patients were given bacteriophage, and five received a polyvalent antistaphylococcus serum prepared by Dr. Lee Foshay. Many patients received combinations of these forms of therapy.

TABLE I

Author	No. of Cases	Mortality	Remarks
Baker and Shands, 1939.....	30	70%	Staphylococcemia with osteomyelitis. "Routine" treatment.
Baker and Shands, 1939.....	35	25.7%	Staphylococcemia with osteomyelitis, treated with staphylococcus antitoxin.
Baker and Shands, 1939.....	36	60%	Cases other than osteomyelitis. Treatment expectant or surgical.
Baker and Shands, 1939.....	12	75%	Treatment expectant or surgical, plus staphylococcus antitoxin.
Dolman, 1934.....	32	78.1%	Staphylococcemia not associated with osteomyelitis. Staphylococcus antitoxin.
Dolman, 1934.....	32	32.3%	Staphylococcemia with osteomyelitis. Staphylococcus antitoxin.
Stookey and Scarpellino, 1939..	117	91.4%	No cases of osteomyelitis. Assorted treatment.
Stookey and Scarpellino, 1939..	17	53%	No cases of osteomyelitis. Staphylococcus antitoxin.
Julianelle, 1939.....	17	57%	Staphylococcus antiserum.
MacNeal and Frisbee, 1936....	100	75%	Treated with bacteriophage.
Dutton, 1933.....	12	8.3%	Treated with bacteriophage.
P. S. MacNeal, 1939.....	9	33.3%	Treated with bacteriophage.
Gilbert, 1938.....	5	20%	Treated with bacteriophage.
Mendell, 1939.....	35	82.9%	Assorted treatment.
Lowenstein, 1931.....	18	77.7%	Supportive treatment.

Autopsies were performed in 16 of the fatal cases, including the two treated with thiazole compounds. The distribution of metastases is shown in table 2, and conforms, in general, with that ordinarily observed.

The four recovered patients include three cases of osteomyelitis, and one patient whose portal of entry was not definitely determined. All were acutely ill. The patients with osteomyelitis were treated by incision and drainage of the local lesion, followed by immobilization. In addition, they were given blood transfusions, and one patient received antistaphylococcal serum. The fourth recovered patient was a 41-year-old white man who was critically ill with metastases to the skin and conjunctiva; he also gave evidence of osteomyelitis of the left toe, though this infection was not manifest until the patient had been in the hospital several days. His treatment consisted of large doses of sulfapyridine, of transfusions of normal blood, and two transfusions of the blood of a donor previously immunized against several strains of staphylococci by Dr. J. A. Kolmer of Philadelphia.*

* Supplied through the kindness of the Philadelphia Blood Bank.

TABLE II
Distribution of Gross and Microscopic Abscesses Found at Autopsy
in 18 Cases of Staphylococcal Septicemia

Organ	Number of Cases
Kidney.....	15
Myocardium.....	8
Lung.....	9
Spleen.....	8
Brain.....	5
Liver.....	5
Heart valves (mitral 5; aortic 2; tricuspid 1).....	5
Intestine (ulcerative enteritis).....	3
Pericardium.....	2
Mediastinal tissue	1
Endometrium	
Myometrium	
Parametrium	
Prostate	
Psoas muscle	
Perinephric fat	

His improvement was gradual but definite, though it was difficult to ascribe it to any one therapeutic measure. Three positive blood cultures were obtained when the sulfapyridine blood level varied between 6 and 13 mg. per cent, and one positive culture was obtained four days after the immunotransfusion. He was well five months after discharge.

REPORT OF PATIENTS TREATED WITH THIAZOLE DERIVATIVES

Case 1. This 14-year-old schoolboy was admitted to the Cincinnati General Hospital January 27, 1940, complaining of fever and malaise of four days' duration. A week before admission he had twisted his leg in the rung of a rocking chair, and six

TREATMENT AND LABORATORY TESTS

Case 1

Date	Blood Cultures	SMT Grams	SMT Blood Levels *	Blood Transfusions	Remarks
1-27-40	Non-hem. <i>Staph. aureus</i> 23 col./c.c.	5		500 c.c.	Incision and drainage— left tibia; cast applied. Pus from rt. zygoma = <i>S. aureus</i> . Pus from left tibia = <i>S. aureus</i> .
1-28-40	Non-hem. <i>Staph. aureus</i> 26 col./c.c.	5	Total: 2.5 mg. % Free: 0.9 mg. %	250 c.c.	
1-29-40	Neg.	7	Total: 2.0 mg. % Free: 0.6 mg. %	300 c.c.	
1-30-40	Neg.	11	Free: 0.8 mg. %		
1-31-40	Neg.	11	Free: 0.8 mg. %		
2- 1-40		12			
2- 2-40	Neg.	12	Free: 1.5 mg. %		
2- 3-40		9		250 c.c.	
2- 6-40				250 c.c.	

SMT = Sulfamethylthiazole.

Total Grams SMT = 72.

* Blood levels were determined by the method of Bratton and Marshall. Early determinations were read against a sulfapyridine standard and corrected for molecular weight; later sulfamethylthiazole was used as a standard.

days later the leg became swollen and tender. That day he had several chills. He noticed at the same time that the right side of his face was swollen and tender.

Physical examination revealed an acutely ill boy with a temperature of 101.8° F., pulse 120, respirations 20, and blood pressure 120 systolic and 88 diastolic. There was a red, tender, swollen area over the right zygoma. The left leg was swollen and tender from the ankle to the knee. The remainder of the physical examination was not remarkable.

The white blood cells numbered 22,000, the red blood cells numbered 4.34 million, and the hemoglobin 12.5 grams per cent. Blood culture yielded 23 colonies per cubic centimeter of a non-hemolytic *Staphylococcus aureus*.

Treatment consisted of oral sulfamethylthiazole, blood transfusions, and surgical intervention. An incision and drainage were performed at two points on the tibia, pus aspirated, and a cast applied. Another incision was made beneath the periosteum of the right zygoma, and pus removed. The relation between blood cultures and treatment is shown in the accompanying table.

The patient returned home with the left leg in a cast two weeks after admission. He later returned to the hospital, and six weeks after his first discharge from the hospital underwent a sequestrectomy. The lesion in the zygoma area healed during the first admission.

TREATMENT AND LABORATORY TESTS

Case 2

Date	Blood Cultures	SMT Grams	SMT Blood Levels	Blood Transfusions	Remarks
2-19-40	<i>Staph. aureus</i>				Incision and drainage—left humerus. Sub-periosteal pus yielded <i>Staph. aureus</i> .
2-20-40	<i>Staph. aureus</i> 1:00 p.m. 4 col. 8:30 p.m. neg. 10:45 p.m. neg.	4			
2-21-40	Neg.	24	6.3 mg. %	300 c.c.	
2-22-40		24	7.9 mg. %	500 c.c.	
2-23-40	Neg.	24		250 c.c.	Cast applied.
2-24-40		24	8.2 mg. %		
2-25-40		18			
2-26-40		6			
2-27-40		6	2.6 mg. %		
2-28-40		5			
2-29-40		4			
3- 1-40		6	3.9 mg. %		
3- 2-40		6			
3- 3-40		6			
3- 4-40		6			
3- 5-40		6			
3- 6-40		4			

SMT = Sulfamethylthiazole.
Total Grams SMT = 173.

Case 2. This 19-year-old messenger boy was admitted to the Cincinnati General Hospital on February 18, 1940, complaining of pain in the left arm and shoulder of eight days' duration. Eleven days before admission he had been aware of some "stiffness" of the left elbow, but had no pain at that time. Three days later, pain and swelling appeared in the left elbow and shoulder, pain that was aggravated by movement or palpation. The following day he had a chill. During the succeeding week, his temperature ranged from 102° to 104°. The boy was acutely ill, and suffered from nausea and vomiting.

On admission to the hospital, the temperature was 104.4°, the pulse 120, the respirations 24, and the blood pressure 136 systolic and 78 diastolic. He was acutely ill. Important physical findings were limited to the left upper extremity. There was some swelling of the entire left arm, from the wrist to the shoulder, but the maximum swelling and tenderness involved the upper arm. There were a few small discrete tender axillary nodes on the left.

The red blood cell count was 5.06 million, the hemoglobin was 13.4 grams per cent, and white blood cells numbered 14,400, with 85 per cent neutrophils. The admission blood culture showed 92 colonies of *Staphylococcus aureus* per cubic centimeter. A roentgen-ray on February 20 showed evidence of osteomyelitis of the left humerus with slight periosteal elevation.

TREATMENT AND LABORATORY TESTS

Case 3

Date	Blood Cultures	SMT Grams	Blood Levels Free—mg. %	Blood Transfusions
2-15-40	<i>S. aureus</i> (Hemolytic)	3		
2-16-40		24		200 c.c.
2-17-40	<i>S. aureus</i> 1 col./c.c.	24	7.3	500 c.c.
2-18-40	<i>S. aureus</i> 2 col./c.c.	24	10.8	200 c.c.
2-19-40	<i>S. aureus</i> 2 col./c.c.	24	6.3	200 c.c.
2-20-40	<i>S. aureus</i> 1 col./c.c.	24	8.5	200 c.c.
2-21-40	<i>S. aureus</i> Plate neg.	24	9.5	200 c.c.
2-22-40	Neg.	24	7.0	200 c.c.
2-23-40	Neg.	24	8.7	200 c.c.
2-24-40	Neg.	6	9.0	200 c.c.
2-25-40		6	5.7	
2-26-40	Neg.	6	6.8	200 c.c.
2-27-40	Neg.	3	6.0	200 c.c.
2-28-40	Neg.	3	3.4	
2-29-40		3		
3- 1-40		3		
3- 2-40	Neg.	3	2.6	
3- 3-40		3		
3- 5-40	Neg.			

SMT = Sulfamethylthiazole.

Total Grams SMT = 231.

On the morning of February 20, the patient was started on sulfamethylthiazole. The same day incision and drainage were performed upon the left humerus and a large amount of subperiosteal pus containing staphylococci removed. The relation between cultures and therapy is shown in the accompanying table. Improvement was rapid at first, more gradual after the first few days. The temperature did not reach normal levels for three weeks. Sulfamethylthiazole was continued for six days following the operation. On March 1, a cast was applied to the arm, and a week later the patient was discharged. He was re-admitted to the hospital a month later to have the cast changed. At that time, roentgen-ray showed evidence of active subacute osteomyelitis, but no evidence of sequestration. By July 15, however, the local process had become so extensive that nearly all of the humerus had been destroyed.

Case 3. (Reported by courtesy of Drs. Richard Tyler and Ashton Welsh.) This patient was admitted to the Good Samaritan Hospital on February 5, 1940, complain-

ing of a carbuncle of the nose. Two weeks before admission, he had pulled a hair from the edge of the nares. Several days later the nose became red, tender, and swollen. Hot packs applied to the nose brought about no improvement, so the patient was brought to the hospital. He was a mild diabetic.

On admission to the hospital, the patient was acutely ill. The nose was swollen, deep purple, tender, and painful. The medial portion of the eyelids was swollen. The remainder of the physical examination was negative.

The hemoglobin was 82 per cent and the white blood cells numbered 15,850. The urine contained sugar, but no acetone. The blood sugar was 416 mg. per cent, and the CO₂ combining power 55 volumes per cent. Culture of pus from the nose yielded a hemolytic *Staphylococcus aureus*.

TREATMENT AND LABORATORY TESTS

Case 4

Date	Blood Cultures	SFMD Grams	SFMD Blood Levels	Blood Transfusions
2-22-40	Neg.			500 c.c.
2-23-40	Neg.			1000 c.c.
2-24-40		5		280 c.c.
2-25-40		6		250 c.c.
2-26-40		6	6.0 mg. %	200 c.c.
2-27-40		6	10.4 mg. %	250 c.c.
2-28-40		2		250 c.c.
2-29-40	<i>Staph. aureus</i>			250 c.c.
3- 1-40		SFPD	SFPD	
3- 2-40	<i>Staph. aureus</i>	2	Faint trace	270 c.c.
3- 3-40		6		250 c.c.
3- 4-40		6	5.2 mg. %	250 c.c.
3- 5-40		5	13.8 mg. %	250 c.c.
3- 6-40		4		
		4	12.1 mg. %	
3- 7-40	<i>Staph. aureus</i>	SMT		
	17 col.	4	Free 4.8 mg. %	
3- 8-40	<i>Staph. aureus</i>	9	Total 5.7 mg. %	
	49 col.		7.9 mg. %	250 c.c.
3- 9-40	<i>Staph. aureus</i>	9	6.3 mg. %	500 c.c.
	108 col.			
3-10-40		9		
3-11-40	<i>Staph. aureus</i>	9		
	73 col.			
3-12-40	<i>Staph. aureus</i>	4.5		
	824 col.			

SFMD = Sulfanilamide.

SFPD = Sulfapyridine.

SMT = Sulfamethylthiazole.

Total Grams SMT = 44.5.

Despite roentgen-ray treatment and local magnesium sulfate compresses, the infection spread and on February 15, a blood culture yielded a hemolytic *Staphylococcus aureus*. Sulfamethylthiazole was begun the following day; the relation between blood cultures and therapy is shown in the accompanying table. The patient improved gradually, and was finally allowed out of bed on April 2. At that time, a bilateral foot drop was observed, and a neurological examination revealed that the knee jerks were diminished in both legs, and the ankle jerks absent. Muscle weakness was restricted to the feet. Vibratory, position, and pain perception were normal.

Case 4. This 32-year-old white woman was admitted to the obstetrical service of the Cincinnati General Hospital on February 20, 1940, in the seventh month of pregnancy, with a placenta praevia. A Brown bag was inserted, but removed at the end of

12 hours. At this time the membranes were ruptured and another bag inserted. Several hours later, a Braxton-Hicks version was performed and a dead fetus delivered. The placenta did not separate and had to be removed manually. Intra-uterine and intravaginal packs were inserted. During the version, the patient had a chill, followed by elevation of her temperature to 105.6°. The patient was given sulfanilamide, 6 grams a day, for four days. Sulfapyridine was substituted but she continued to grow worse. She received 1 gram every 4 hours for six days, but showed no improvement. At the end of this period the patient was transferred to the medical service and sulfamethylthiazole begun. She was very ill, showed signs of patchy pneumonia with dyspnea and cyanosis, went rapidly down hill, and died six days after the institution of sulfamethylthiazole. The day before death, a pericardial friction rub was heard. The relation between the patient's course and treatment is shown in the accompanying table.

Postmortem examination showed acute suppurative endometritis and myometritis with retained placental polyp; miliary abscesses in the wall of the uterus; acute pyometritis; acute vegetative endocarditis of the mitral and tricuspid valves; miliary abscesses in the myocardium, lungs, and kidneys; purulent pericardial effusion with fibrino-purulent pericarditis; septic infarction of the spleen.

Case 5. (Reported through the courtesy of Drs. Leon Schiff and Joseph P. Evans.) This 28-year-old housewife was admitted to the Holmes Hospital on March 31, 1940, complaining of pain in the neck of nine days' duration. She had been in good health until nine days before admission, when she developed pain in the posterior cervical region, and limitation of motion in all directions. This pain gradually increased in severity, and radiated down the neck along the trapezii and down the arms to some extent. She had no chills. The temperature ranged from 99° to 101°. For two days before admission she received sulfanilamide, 4 grams a day.

On admission to the hospital she was acutely ill, cyanotic, and moderately drowsy. Temperature was 100.4°, pulse 104, and respirations 20. The neck was stiff, with marked tenderness over the cervical spines, greatest over the seventh spine. There was some tenderness laterally with spasms of the neck muscles posteriorly, including the trapezii. The remainder of the physical examination was negative.

The red blood cells numbered 3.59 million, the hemoglobin 10 grams per 100 c.c., and the white blood cells 13,700. Differential blood count showed 81 per cent neutrophils, 13 per cent lymphocytes, and 5 per cent monocytes. Urine had a specific gravity 1.018, albumin one plus, and 10-12 white blood cells per high power field.

A tentative diagnosis of cervical osteomyelitis was made, though the only roentgen-ray evidence was the presence of thickening of the prevertebral fascia. She was given sulfanilamide. When a blood culture taken the day after admission revealed *Staphylococcus aureus*, the sulfanilamide was stopped, and sulfamethylthiazole begun. On April 1, the patient developed meningitis, and *Staphylococcus aureus* was recovered from the cerebrospinal fluid.

She was critically ill for several days. Stupor developed and the Kernig sign was present. The cell count in the spinal fluid rose to 1100 cells, of which the majority were polymorphonuclears. Hemolytic *Staphylococcus aureus* was recovered from the spinal fluid on four different days, and on one occasion cocci were found on the direct smear of the fluid. The patient received sulfamethylthiazole during this period, and the relationship between dosage, cultures and blood levels is shown in the accompanying table. Improvement was gradual but definite, and by April 9 her improvement was very distinct. On April 11, a generalized maculopapular rash appeared, sulfamethylthiazole was discontinued, and within two days the rash had vanished. A lumbar puncture performed on April 11 revealed evidence of probable block in the spinal canal, and six days later the block was complete. On April 19 roentgen-ray showed evidence of osteomyelitis of the fourth and fifth cervical verte-

brae, and a cast was applied to the neck. The following day, however, she developed numbness and definite weakness of the right arm and leg with loss of appreciation of pin prick in the distribution C4, 5, on that side, and over all the dermatomes of the left arm. A laminectomy involving the arches of C4, 5, 6, and

TREATMENT AND LABORATORY TESTS

Case 5

Date	Blood Culture	SMT Grams	Blood Levels mg. %	Blood Transfusions	C.S.F. Culture	Remarks
3-31-40	<i>S. aureus</i>					
4-1-40	Neg.	4			<i>S. aureus</i>	
4-2-40	<i>S. aureus</i>	4		500 c.c.		C.S.F.: 450 cells.
4-3-40		8	2.0	500 c.c.		
4-4-40		12	Less than 1		<i>S. aureus</i>	
4-5-40	Neg.	15	1.4	250 c.c.		
4-6-40	Neg.	18	3.6	250 c.c.	<i>S. aureus</i>	C.S.F.: 1100 cells.
4-7-40		18	3.2			
4-8-40	Neg.	18	3.2	250 c.c.	<i>S. aureus</i>	C.S.F.: 130 cells.
4-9-40		18	3.6	250 c.c.		
4-10-40		14				
4-11-40		12				1.0 mg. % (SMT. Level in C.S.F.) Rash.
4-12-40	Neg.					
4-16-40	Neg.					
4-17-40						C.S.F. complete block. Laminectomy with bony decompression.
4-20-40		8				
4-21-40		18				
4-22-40		15	3.0			
4-23-40		8				Trace SMT Level in C.S.F.
4-24-40		4	1.8			
4-25-40				250 c.c.		Signs of probable peripheral neuritis.

SMT = Sulfamethylthiazole.

C.S.F. = Cerebrospinal Fluid.

Total Grams SMT = 194.

part of C3 was performed by Dr. J. P. Evans. Postoperative improvement was slow. On April 25, stocking anesthesia of both legs extending 5 cm. above the knees was noted and attributed to sulfamethylthiazole which had been resumed at the time of the laminectomy. The drug was again discontinued. The neurological signs on discharge were limited entirely to pyramidal tract disturbances and a suggestive level of hypesthesia, both subjective and objective, below the level of T8, bilaterally. She still had some numbness in the right arm and hand in addition to that which was present below T8. Strength for walking was adequate and proprioceptive sense was present.

Case 6. This 45-year-old painter was in good health until he fell off a scaffold on April 27, 1940, fracturing his nose and left arm. He was brought to the Cincinnati General Hospital where the fractured nose was set. Examination of the left arm revealed a small laceration on the lateral aspect of the elbow, with shortening of the arm and posterior displacement of the elbow. There was moderate swelling of the soft tissues. The arm was set and the patient put to bed.

On admission the temperature was 99.4°, pulse 76, respirations 18, and blood pressure 130 systolic and 70 diastolic. Though the patient was not at all ill in appearance, he ran a fever of 100-102° for a week. The temperature then fell to normal

for another week. At the end of that time, it was deemed advisable to perform an open reduction of the elbow. The day following the operation the temperature again rose to 102°, and fluctuated between normal and febrile levels for 11 days. Ten days after the operation, a wound infection was discovered, and a culture of the pus yielded

TREATMENT AND LABORATORY TESTS

Case 6

Date	Blood Cultures	ST Grams	ST Blood Levels Free—mg. %
5-19-40	<i>Staph. aureus</i> 1 col./c.c.	6	
5-20-40	<i>Staph. aureus</i> 2 col./c.c.	12	3.3
5-21-40		12	5.9
5-22-40		12	6.8
5-23-40		6	6.0
5-24-40		5	
5-25-40		0	

ST = Sulfathiazole.

Total Grams ST = 53.

Staphylococcus aureus. The following day, the patient suffered definitely chilly sensations, but no frank chill. Blood culture taken the next day yielded *Staphylococcus aureus* in broth, and one colony per cubic centimeter of blood on a plate. He was started on sulfathiazole. The relation between blood cultures and treatment is shown in the accompanying table. The patient made an uneventful recovery, the fever gradually subsided, and a week after discharge from the hospital felt well. At that time, the discharge from the wound had cleared considerably.

Case 7. (Reported through the courtesy of Dr. S. Taplitz.) This 67-year-old farmer was admitted to the Bethesda Hospital on June 3, 1940, in a semi-comatose condition. He had been in excellent health until a month before admission, when he

TREATMENT AND LABORATORY TESTS

Case 7

Date	Blood Cultures	Drug	Blood Level	Remarks
6-3-40	Hem. <i>St. aureus</i> 259 col./c.c.	Sod. SFPD, 4 gm. I.V.	23 mg. %	Staph. antitoxin 60,000 units.
6-4-40	Hem. <i>St. aureus</i> 536 col./c.c.	Sod. SFPD, 5 gm. I.V. Sod. ST. 5 gm. I.V.	22 mg. %	C.S.F.—sterile; 33 cells.
6-5-40	Hem. <i>St. aureus</i> 3870 col./c.c.	Sod. ST 5 gm. I.V.	18.2 mg. %	

SFPD = Sulfapyridine.

ST = Sulfathiazole.

C.S.F. = Cerebrospinal Fluid.

I.V. = Intravenously.

began to complain of malaise. Nevertheless he continued to work until five days before admission. That day he noticed a small discolored swelling on the right little finger, which he thought was due to a splinter. His wife opened the swelling with a

flamed needle. However, the patient's physician noticed similar areas on the toes the same day. The day before admission he became semi-comatose, developed rapid, deep respirations, and was admitted to the hospital.

On physical examination, the temperature was found to be 103° F., the pulse rate 110, and the respirations 25. There were questionable petechiae on the legs, under the finger nails, and on the soles of the feet. The neck was stiff. No cardiac murmurs were heard, but auricular fibrillation was present. The abdominal wall did not relax well, but no organs were felt.

The patient lived only two days after admission to the hospital. The day of admission he was given 4 grams of sodium sulfapyridine intravenously and 60,000 units of commercial staphylococcus antitoxin. The following day he was worse. The white blood cells numbered 21,000, with 89 per cent polymorphonuclears. The spinal fluid was clear and sterile on culture, but contained 33 cells per cubic millimeter. He was given another intravenous injection of 4 grams of sodium sulfapyridine, following which the treatment was changed to intravenous sodium sulfathiazole. The relationship between treatment and blood cultures is shown in the accompanying table.

Autopsy revealed acute vegetative endocarditis of the aortic valve, with perforation of the right posterior cusp. Abscesses were found in the myocardium, spleen, and kidneys. The cranial cavity was not opened.

Case 8. This 45-year-old taboparetic colored woman was admitted to the medical service of the Cincinnati General Hospital on July 1, 1940, because of dysuria, frequency, suprapubic and back pain, and chills of several days' duration. Several months previously, an arthrodesis had been performed on the patient's right knee, to correct a Charcot joint, and at the time of admission to the medical service, the right leg was still in a cast.

The temperature was 103°, pulse 110, respirations 30, and blood pressure 120 systolic and 70 diastolic. The patient exhibited moderate discomfort, but did not appear seriously ill. The heart and lungs were normal. There was definite bilateral costovertebral tenderness. The white blood count was 13,850, the red blood count 4,700,000, and the hemoglobin 15 grams. The urine was cloudy, contained 12 pus cells per high power field, and a small amount of albumin; culture yielded *E. coli*. The blood urea nitrogen was 21 mg. per cent.

On July 12, cystoscopy was performed. Though evidence of chronic cystitis was found, retrograde pyelograms were normal. The following day, the patient had a chill, and a blood culture yielded *Staphylococcus aureus*. The patient was started on sulfathiazole: the relationship between therapy and blood cultures is shown in the accompanying table. Several days later, she complained, for the first time, of pain in the right knee; the cast was removed, and though there was no evidence of osteomyelitis, 270 c.c. of purulent material containing *Staphylococcus aureus* were removed from the joint. The patient was transferred to the orthopedic service, where a through-and-through drainage of the joint was established. The joint continued to drain though the amount of drainage decreased over a period of several weeks.

During an investigation of a complaint of abdominal pain on August 12, a roentgen-ray revealed an infectious process involving L2 and L3, with destruction of large portions of these vertebrae. Nevertheless, the patient was afebrile and improved symptomatically. She left the hospital against advice on August 29.

Case 9. This 55-year-old white man had been perfectly well until about 11 days before admission to the hospital when he developed an influenza-like illness characterized by fever, malaise, generalized aching, and chilly feelings. Several days later a swollen tender area on the left fifth toe was incised by a physician, and a small amount of pus released. Whether this lesion began before or after the onset of generalized symptoms could not be determined. During the days preceding admission the patient noticed small papular lesions on the trunk, face, and extremities.

TREATMENT AND LABORATORY TESTS

Case 8

Date	Blood Cultures	Grams—Drug	Blood Level (Free)	Remarks
7- 2-40		SFMD—.67 gm.		
7- 3-40		SFMD—.33 gm.		
7- 4-40		SFMD—4 gm.		
7- 5-40		SFMD—3 gm.	4.7 mg. %	550 c.c. blood. SFMD discontinued.
7-12-40	<i>Staph. aureus</i>			
7-13-40				350 c.c. blood.
7-14-40	<i>Staph. aureus</i> 18 col.	ST—5		300 c.c. blood.
7-15-40	Non-hemolytic <i>Staph. aureus</i> 4 col.	ST—6	3.0	Knee joint fluid (<i>Staph. aureus</i>).
7-16-40		ST—5	2.4	
7-17-40	<i>Staph. aureus</i> 1 col.	ST—6	3.8	
7-18-40		ST—6		Knee drainage smear; clusters of gram positive cocci.
7-19-40	<i>Staph. aureus</i> 4 col.	ST—5		
7-20-40		ST—2	2.1	Drainage, right knee.
7-21-40		ST—1		
7-22-40	Neg.	ST—5	2.8	
7-23-40	Neg.	ST—6		
7-24-40		ST—6	3.3	
7-25-40	Neg.	ST—5		500 c.c. blood.
7-26-40		ST—5	4.3	
7-27-40		ST—5		
7-28-40	Neg.	ST—6		
7-29-40		ST—6	3.6	
7-30-40		ST—6		
7-31-40		ST—5	3.6	
8- 1-40	Neg.	ST—6		
8- 2-40		ST—5	3.3	
8- 3-40		ST—6		
8- 4-40		ST—3		
8- 5-40				No chemotherapy after 8-5-40.
8- 8-40	Neg.			

SFMD = Sulfanilamide.

ST = Sulfathiazole.

Total Grams ST = 111.

On admission, the patient appeared moderately but not critically ill. The temperature was 103.6°, pulse 112, respirations 36, and the blood pressure 106 systolic and 56 diastolic. Numerous small lesions, macular, papular, and pustular, were present on the trunk and extremities, including the palms and soles. There was an indurated, slightly tender, discolored lesion in the subcutaneous tissue of the left fifth toe; no pus exuded from the area. The breath sounds were suppressed at both lung bases, but no râles were heard. The heart sounds had a scratchy quality, and a soft systolic murmur was heard at the apex; no diastolic murmur was heard. The remainder of the examination was essentially negative.

The patient was given sulfathiazole by mouth, even before blood cultures were reported positive for *Staphylococcus aureus*. When there was no response to the drug, sulfamethylthiazole was substituted, but this agent was equally ineffective. The patient

TREATMENT AND LABORATORY TESTS

Case 9

Date	Blood Cultures	Grams—Drug	Blood Level (Free)	Remarks
8-29-40	Hem. <i>Staph. aureus</i> 282 col.	ST—2		
8-30-40	Hem. <i>Staph. aureus</i> 345 col. (9:30 a.m.) 217 col. (4:45 p.m.)	ST—10	3.4 mg. %	Blood transfusion 500 c.c.
8-31-40	Hem. <i>Staph. aureus</i> 555 col.	ST—2 SMT—5	5.0 mg. %	
9- 1-40	Hem. <i>Staph. aureus</i> 405 col.	SMT—9	5.0 mg. %	

ST = Sulfathiazole.
SMT = Sulfamethylthiazole.
Total Grams ST = 14.
Total Grams SMT = 14.

went rapidly down hill and died on the fourth hospital day. The relationship between therapy and blood cultures is shown in the accompanying table.

Autopsy revealed acute vegetative endocarditis of the mitral valve, with metastatic abscesses in the lungs, liver, spleen, kidneys, perinephric fat, small intestine, brain, and skin. In addition, there was inflammation of the subcutaneous tissue of the small toe of the left foot.

Case 10. This 60-year-old miner was admitted to the Cincinnati General Hospital with a 10-day history of chills, fever, sweats, cough, and pain in the right shoulder. He remained in bed during that period, and gradually became worse. For three months before, he had had a non-productive cough.

TREATMENT AND LABORATORY TESTS

Case 10

Date	Blood Cultures	Grams—Drug	Blood Level (Free)	Remarks
10-15-40		0		
10-16-40		SFPD—2		Blood urea nitrogen 65 mg. %.
10-17-40	<i>Staph. albus</i> innumerable	SFPD—4		Urine cult. = <i>S. albus</i> .
10-18-40	<i>Staph. albus</i> innumerable	ST—3		Blood urea nitrogen 87 mg. %.
10-19-40	<i>Staph. albus</i> 178 col./c.c.	ST—6	4.9 mg. %	Bursal fluid = <i>S. albus</i> .
10-20-40	<i>Staph. albus</i>	ST—6	6.8 mg. %	Blood urea nitrogen 98 mg. %.
10-21-40	<i>Staph. albus</i> 92 col./c.c.	ST—6	12.5 mg. %	Blood urea nitrogen 65 mg. %.
10-22-40	<i>Staph. albus</i> 54 col./c.c.	ST—6	13.7 mg. %	Blood transfusion 500 c.c. Blood urea nitrogen 115 mg. %.
10-23-40		ST—1		

SFPD = Sulfapyridine.
ST = Sulfathiazole.
Total Grams SFPD = 6.
Total Grams ST = 28.

On physical examination he was found to be acutely ill, confused, and poorly nourished. The temperature was 102°, the pulse 100, the respirations 36, and the blood pressure 110 systolic and 60 diastolic. The heart was considerably enlarged, and a loud systolic murmur was heard all over the precordium, especially loud at the apex. There were râles at both lung bases and in the left axilla. The liver descended four fingers'-breadth below the costal margin. There was a large hard mass in the left flank believed to be the kidney. The right shoulder was painful on motion.

The red blood count was 4.34 million, the hemoglobin 12.4 grams, and the white blood count was 15,800 with 72 per cent polymorphonuclear neutrophils. The urine was cloudy, contained two plus albumin, 5 to 15 white blood cells per high power field, innumerable red blood cells and occasional casts. The Kahn reaction on the blood serum was negative. The blood urea nitrogen was 65 mg. per cent, the CO₂ combining power 33 volumes per cent. Blood culture revealed thousands of colonies of *Staphylococcus albus* per cubic centimeter.

Before the results of the blood culture were known, the patient was given sulfa-pyridine, but sulfathiazole was substituted as soon as the staphylococci were recovered. The relation between blood cultures and treatment is shown in the accompanying table.

The course of the patient was rapidly downhill. Petechiae appeared on the trunk and legs, as well as on the conjunctivae. The systolic murmur noted on admission became louder. He died on the eighth hospital day.

Autopsy revealed acute vegetative endocarditis of the mitral valve, multiple miliary abscesses of the kidneys, unresolved pneumonia of the right lower lobe, cirrhosis of the liver, and acute toxic splenitis.

Case 11. This 71-year-old white man was ostensibly in good health until eight days before admission when he complained to his wife of pain in the right knee on standing or walking. A few days later he began to suffer from pain in the right hip. The next day he had several chills, followed by fever. For several months he had had symptoms of mild diabetes.

Physical examination revealed an acutely ill, but fairly well nourished old man who was somewhat irrational. The temperature was 104°, the pulse 116, respirations 26, and blood pressure 170 systolic and 90 diastolic. There were no skin lesions. Most of the teeth had been removed. The lungs were clear. The heart was moderately enlarged to the left, and a soft systolic murmur was heard at the apex. The right leg was held flexed at the hip and knee. The knee could be passively extended but only with considerable pain. Movement of the right hip joint in any direction caused pain. There was no redness, swelling, or local heat about either joint, though palpation over the posterior aspect of the hip joint caused sharp pain.

The red blood count was 4.9 million, and the hemoglobin 15 grams. The white blood count was 33,000, with 87 per cent neutrophils. The urine contained four plus sugar and a trace of acetone, but was otherwise negative. The blood sugar was 308 mg. per cent, and the carbon dioxide combining power 40 volumes per cent. Blood culture yielded a non-hemolytic *Staphylococcus aureus*, 25 colonies per cubic centimeter. Roentgen-rays of the right knee and hip did not show evidence of osteomyelitis or pyarthrosis.

Sulfathiazole was begun on the third hospital day and continued for two weeks. The relationship between course and treatment is shown in the accompanying table. The patient's course was one of gradual improvement. On the second hospital day, one cubic centimeter of staphylococcus containing pus was aspirated from deep in the right gluteal region, but whether the pus came from the joint or from the soft tissues could not be ascertained. Further attempts at aspiration in the same region proved unsuccessful. After two weeks chemotherapy was discontinued, but the patient continued to have low grade fever, and though several consecutive blood cultures had been negative, a culture taken two weeks later yielded 15 colonies of staphylococci

TREATMENT AND LABORATORY TESTS

Case 11

Date	Blood Cultures	Grams— Drug (ST)	Blood Level (Free)	Remarks
9-14-40	<i>Staph. aureus</i> 25 col.			Pus from gluteal abscess (<i>Staph. aureus</i>).
9-15-40				
9-16-40	Non-hemolytic <i>Staph. aureus</i> 19 col.	7		
9-17-40	2 col.	6		
9-18-40	1 col.	6		
9-19-40	Neg.	6		
9-20-40	Neg.	6		
9-21-40	Neg.	6	3 mg. %	
9-22-40	Neg.	6		
9-23-40	Neg.	6	4.8 mg. %	
9-24-40	Neg.	6		
9-25-40		6	3.4 mg. %	
9-26-40	Neg.	6	3.9 mg. %	
9-27-40		6		
9-28-40		6	4.5 mg. %	
9-29-40		6		
9-30-40		1	1.8 mg. %	
10- 1-40	Neg.			
10- 2-40	Neg.			
10-15-40	<i>Staph. aureus</i> 6 col.	6		
10-16-40		6		
10-17-40		6	2.6 mg. %	
10-18-40		6		
10-19-40		6	6.6 mg. %	
10-20-40		6		
10-21-40	Neg.	6	3.4 mg. %	Urine—Non-hem. strep. <i>B. coli</i> .
10-22-40		6		
10-23-40		6		
10-24-40		6	2.6 mg. %	
10-25-40		6		
10-26-40		6	3.2 mg. %	
10-27-40		6		
10-28-40		2	5.0 mg. %	
10-31-40	Neg.			ST discontinued.

ST = Sulfathiazole.

Total Grams ST = 166.

per cubic centimeter. Sulfathiazole was given again with prompt sterilization of the blood stream. No new local foci appeared during this recrudescence. The drug was continued another two weeks when a bilateral conjunctivitis warranted its discontinuance. This complication disappeared as soon as the sulfathiazole was discontinued, but reappeared the following week when the patient was given the drug again. Improvement was steady, and the patient was discharged to a convalescent home, asymptomatic and afebrile.

Case 12. This 57-year-old housewife was admitted to the Surgical Service of the Cincinnati General Hospital for treatment of a large carbuncle of the neck, of three weeks' duration. She had suffered from diabetes mellitus for over a year, but since the onset of the carbuncle the diabetes had become more difficult to control.

TREATMENT AND LABORATORY TESTS

Case 12

Date	Blood Cultures	Grams—Drug (ST)	Blood Level	Remarks
10-13-40				X-ray therapy.
10-14-40				X-ray therapy—Incision and drainage.
10-15-40				X-ray therapy.
10-16-40				X-ray therapy.
10-17-40	<i>Staph. aureus</i> 11 col./c.c.	7		X-ray therapy.
10-18-40		6		
10-19-40	Neg.	8	3.9 mg. %	500 c.c. blood.
10-20-40	Neg.	6		
10-21-40	Neg.	5	1.9 mg. %	Incision and drainage.
10-22-40	Neg.	7	3.5 mg. %	250 c.c. blood.
10-23-40	Neg.	7		250 c.c. blood.
10-24-40	Neg.	13	3.3 mg. %	250 c.c. blood.
10-25-40		7	7.6 mg. %	250 c.c. blood.
10-26-40				250 c.c. blood.
10-27-40		Na SFPD		250 c.c. blood.
11- 2-40		5		150 c.c. blood. Excision of carbuncle.
11- 3-40	Neg.	5		
11- 4-40		(ST) 3	1.6 mg. %	500 c.c. blood.
11- 5-40		4		250 c.c. blood.
11- 6-40	Neg.	6	1.5 mg. %	250 c.c. blood.
11- 7-40		3		250 c.c. blood.
11- 8-40			Neg.	250 c.c. blood.
11- 9-40				250 c.c. blood.
11-10-40				Excision of carbuncle.
11-11-40				250 c.c. blood.
11-12-40			Trace	250 c.c. blood.
11-13-40		1		
11-14-40		1.5		
11-15-40		1		
11-16-40				

ST = Sulfathiazole.

Na SFPD = Sodium Sulfapyridine.

Total ST = 85.5.

Total Na SFPD = 10.

On physical examination she was found to be acutely ill, with a temperature of 101.6°, pulse of 90, respirations 20, and blood pressure of 110 systolic and 80 diastolic. There was a large carbuncle on the back of the neck, with a linear transverse area of necrosis draining pus. The cervical nodes were slightly enlarged and tender bilaterally. The remainder of the physical examination was essentially negative.

The white blood count was 20,000 and the hemoglobin 17 grams. The urine contained four plus sugar but no acetone. The blood sugar was 333 mg. per cent and the CO₂ combining power 50 volumes per cent.

Roentgen-ray therapy was begun and continued for five days. On the second hospital day, a radical incision and drainage were performed. On the fifth hospital day, because of a chill, a blood culture was taken and sulfathiazole started. The blood at that time was found to contain 11 colonies of *Staphylococcus aureus* per cubic centimeter, but was subsequently sterile. The relationship between cultures and treatment is shown in the accompanying table. Improvement followed, with remission of fever, but a local extension of the process a week later necessitated

another incision and drainage, followed by a radical excision of the carbuncle several days later. At the time of the present report, the carbuncle is healing and progress is considered satisfactory.

DISCUSSION

In the thiazole derivative group, the only deaths that occurred were associated with acute bacterial endocarditis, a condition which still resists the best efforts of the therapist. If these cases are disregarded, the small series represents eight consecutive cases in which clearing of the blood stream took place after invasion by staphylococci. There is no doubt that any or all of these patients might have survived had they received only supportive treatment, for the literature is replete with single case reports of patients who have made remarkable recoveries from this highly fatal disease. Moreover, three of our cases were associated with osteomyelitis. Nevertheless, the recovery of eight consecutive acutely ill patients indicates that the thiazole compounds should be given further trial. Study of these cases adduces no evidence of any effect upon the local lesions.

Some of our experience has been with sulfamethylthiazole, whose toxicity seems to be greater than its non-methylated analogue.¹³ In this series, two cases of peripheral neuritis were observed in patients treated with sulfamethylthiazole, but none in the sulfathiazole series. However, this complication occurred at the beginning of our experience with the drugs, when we were using larger doses than we later found necessary. Whether peripheral neuritis would have occurred had smaller doses been employed we cannot say. The "minor toxicities"—nausea, vomiting, rashes—appeared to be less frequent in patients receiving sulfamethylthiazole.

SUMMARY

1. Twelve consecutive cases of staphylococcal septicemia were treated with thiazole derivatives of sulfanilamide. Eight recovered.
2. In all the fatal cases, endocarditis was present at autopsy.
3. A skin rash and an instance of peripheral neuritis were probably attributable to sulfamethylthiazole. Conjunctivitis and chills and fever were observed as examples of sulfathiazole toxicity.
4. Between the years 1933–1939, 27 cases of staphylococcal septicemia were recorded at the Cincinnati General Hospital, with only four recoveries.

BIBLIOGRAPHY

1. BAKER, L. D., and SHANDS, A. R., JR.: Staphylococcal osteomyelitis with staphylococemia, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2119.
2. DOLMAN, C. E.: Staphylococcus antitoxic serum in the treatment of acute staphylococcal infections and toxemias, *Canad. Med. Assoc. Jr.*, 1934, xxx, 601.
3. STOOKEY, PAUL F., and SCARPELLINO, LOUIS A.: Staphylococcus septicemia, *South. Med. Jr.*, 1939, xxxii, 172.
4. JULIANELLE, L. A.: Observations on the specific treatment (Type A antiserum) of staphylococcal septicemia, *ANN. INT. MED.*, 1939, xiii, 308.

5. MACNEAL, WARD J., and FRISBEE, FRANCES C.: Bacteriophage service to patients with staphylococcus septicemia, Am. Jr. Med. Sci., 1936, cxc, 170.
6. DUTTON, L. O.: The therapeutic use of bacteriophage, with special reference to staphylococcus septicemia, Southwest. Med., 1933, xvii, 374.
7. MACNEAL, PERRY S.: *Staphylococcus aureus* septicemia; a preliminary report, Univ. Hosp. Bull., Ann Arbor, 1939, v, 58.
8. GILBERT, WARREN M.: Staphylococcus septicemia. Treatment with bacteriophage, Jr. Med. Assoc. Ga., 1938, xxvii, 155.
9. MENDELL, THEODORE H.: Staphylococcic septicemia: a review of thirty-five cases, with six recoveries, twenty-nine deaths and sixteen autopsies, Arch. Int. Méd., 1939, lxxiii, 1068.
10. LOWENSTEIN, P. S.: Staphylococcal septicemia, Am. Jr. Med. Sci., 1931, clxxxi, 196.
11. STOOKEY, P. F., SCARPELLINO, L. A., and WEAVER, J. B.: Immunology of osteomyelitis, Arch. Surg., 1936, xxxii, 494.
12. ROBERTSON, D. E.: Acute hematogenous osteomyelitis, Jr. Bone and Joint Surg., 1938, xx, 35.
13. MCKEE, C. M., RAKE, G., GREEP, R. O., and VAN DYKE, H. B.: Therapeutic effect of sulfathiazole and sulfapyridine, Proc. Soc. Exper. Biol. and Med., 1939, xlii, 417-421.
14. BRATTON, A. C., and MARSHALL, E. K., JR.: A new coupling component for sulfanilamide determination, Jr. Biol. Chem., 1939, cxxviii, 537.

PREMONITORY SYMPTOMS OF ACUTE CORONARY OCCLUSION; A STUDY OF 260 CASES *

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THE symptoms of occlusion of the coronary artery are now well known, and the diagnosis of the acute attack is generally made with little difficulty. It is only recently, however, that attention has been paid to prodromes of the attack. Recognition of these premonitory symptoms is important both from a diagnostic and a therapeutic standpoint. Thus, the realization that a sudden onset of chest pain may presage the onset of coronary occlusion within a few hours or days will lead to earlier diagnosis of the impending attack and indicate immediate bed rest. Knowledge of such premonitory pain is essential in attempting to correlate the clinical history or mode of onset of the attack and the pathological findings in the heart, or to evaluate the various theories of the pathogenesis of coronary occlusion.

Premonitory pain or discomfort in the chest prior to an attack of acute occlusion of the coronary artery was mentioned early by several authors,¹⁻⁵ and several cases have been reported^{6, 7} in which there was well marked prodromal pain. A study of the 145 case histories presented by Levine⁸ in his classical monograph reveals that some form of premonitory pain was observed in only twelve. Similarly Bean⁹ reported an incidence of only 9.3 per cent in 300 cases studied by him. On the other hand, Feil¹⁰ estimated that approximately 50 per cent of the cases in his series showed a history of premonitory pain. The low incidence reported by Bean may be due to the fact that his series consisted of autopsy cases collected since 1922, and he had not been able to obtain detailed histories at first hand. This probably applies in part also to the cases of Levine. Feil,¹⁰ Sampson and Eliaser,¹¹ and more recently, Langston,¹² have described in detail the clinical characteristics of the premonitory pain, respectively in 15, 29, and 5 cases of coronary occlusion, and have emphasized their importance.

MATERIAL AND FINDINGS

This study is based on detailed histories which were carefully elicited by the authors in 260 cases of acute coronary occlusion. A questionnaire was especially prepared¹³ concerning the occurrence of angina pectoris previous to the attack, the occurrence of any symptoms as far back as four weeks prior to the attack, and the physical and emotional activities associated with them.

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Character of Premonitory Symptoms. Premonitory symptoms were found to have occurred in 115, or 44.2 per cent of the cases studied. Their character, time of occurrence, and precipitating factors are presented in tables 1 and 2. The most common symptom was substernal or precordial

TABLE I
Premonitory Symptoms in Coronary Occlusion; Their Character and Time of Appearance before the Attack

Symptoms	No. of Cases	Appearance before Attack										
		Less 1 hour	1-6 hours	7-12 hours	12-24 hours	1 day	2 days	3 days	4-6 days	1 week	2 weeks	3 weeks
Chest or precordial pain	26	0	2	2	9	1	5	4	2	1	0	0
Sudden appearance of anginal syndrome	15	0	0	0	0	0	1	1	1	6	4	2
Increasing anginal syndrome on exertion	8	0	0	0	0	0	0	1	1	2	3	1
Chest or precordial discomfort (coldness, heaviness, fullness in chest)	17	0	4	2	4	2	1	0	1	1	2	0
Pain in arms or shoulders	4	1	0	0	1	1	0	0	0	0	1	0
Dyspnea	4	0	0	0	3	0	0	0	1	0	0	0
Palpitation	3	0	0	0	1	0	1	0	0	1	0	0
Fatigue, weakness or "did not feel well"	22	0	4	0	9	1	3	0	1	2	2	0
Gastric symptoms	10	0	4	0	2	0	0	3	1	0	0	0
Nervousness, dizziness, coldness or feeling of heat	6	4	1	1	0	0	0	0	0	0	0	0
Total premonitory symptoms	115	5	15	5	29	5	11	9	8	13	12	3
No premonitory symptoms	145											
Total cases	260											

TABLE II
Precipitating Factors of the Premonitory Symptoms of Coronary Occlusion

Symptoms	No. of Cases	Precipitating Factors (70 cases)					Associated Factors (8 cases)		
		Rest	Mild Activity	Moderate Activity	Walking	Unusual Activity	Excitement	Meals	Cold
Precordial pain	20	7	6	1	3	1	0	2	0
Sudden angina pectoris	7	0	1	2	4	0	0	0	0
Increasing angina pectoris	9	0	0	3	6	0	0	0	0
Precordial discomfort	11	3	1	4	2	1	1	0	0
Pain in arms	4	1	1	0	0	0	0	1	1
Dyspnea	4	2	0	1	1	0	0	0	0
Palpitation	2	2	0	0	0	0	0	0	0
Weakness; "did not feel well"	9	2	2	2	0	0	2	2	0
Gastric symptoms	2	1	1	0	0	0	0	0	0
Nervousness, dizziness, etc.	6	2	1	1	1	0	0	1	0
Total	80	20 (28.5%)	15 (21.4%)	16 (22.8%)	17 (24.3%)	2 (2.9%)	3	6	1

pain, which occurred in 49, or 43 per cent, of the 115 patients (table 1). Seventeen other patients experienced vague discomfort in the chest, such as fullness, heaviness, coldness, or burning. Pain in the arms or shoulders occurred in four patients. In 15 of the 43 patients presenting chest pain, an anginal syndrome developed suddenly on effort or excitement, several days or weeks before the onset of the attack (see case report); in eight

patients an anginal syndrome had been present for some time but there was a sudden increase in the severity and frequency of the pain immediately preceding the attack of occlusion. Other cardiac symptoms noted prior to the attack were dyspnea (four cases) and palpitation (three cases).

A large group of cases presented prodromes other than cardiac pain. Twenty-two patients noted fatigue or weakness or "did not feel well," and 10 suffered gastric symptoms such as nausea, epigastric distress, a sensation of fullness, or abdominal pain. Occasional miscellaneous symptoms included nervousness, dizziness, and a feeling of coldness or of warmth (6 cases).

Time of Onset and Duration of Symptoms. In half the cases, the premonitory symptoms appeared within 24 hours of the acute attack (table 1). In a little over one-third they occurred from two to seven days, and in the remainder from two to three weeks before the occlusion. Among the 23 patients who developed angina on effort, the symptoms often appeared several days or weeks preceding the attack. In eight cases they preceded it by one week, in seven cases by two weeks, and in three cases by three weeks. In the series of Sampson and Eliaser premonitory pain appeared from three to five weeks prior to the occlusion in two of the 29 cases.

The duration of the premonitory symptoms varied. In many cases there was a single attack of pain lasting from a few minutes to several hours, after which the patients would be free of pain until the onset of occlusion. In others the seizures of pain or discomfort were transient and recurrent, and not infrequently the pain was continuous for several hours or days. The duration of the warning attack in the series of cases reported by Sampson and Eliaser also varied from a few minutes up to 14 hours. In Feil's series the premonitory pain lasted from 12 to 48 hours in eight of the 15 cases and from three to four weeks in two cases.

Precipitating Factors. The activity of the patients immediately preceding the premonitory attack could be elicited in 70 of our 115 cases. (Table 2.) The onset occurred during rest in 28.5 per cent of the cases, during mild activity in 21.4 per cent, during moderate activity in 22.8 per cent, and while walking in 24.3 per cent. In no one case did the symptoms begin during sleep, but several patients were aware of pain immediately upon rising. Unusual exertion occurred in only two cases (2.9 per cent). In 10 other cases the onset was associated with a secondary factor such as meals (six cases), excitement (three cases), and cold (one case). Mild activity included routine activities at home, standing in the street, sitting at a meeting, etc. Moderate activity included working, shopping, fishing, etc. The two instances of unusual activity were shoveling snow and an automobile accident. In the three cases associated with excitement, two patients were attending a wedding and one was suffering from anxiety.

Case Report. The following case of acute coronary occlusion was characterized by a prodromal period of five days' duration, during which the im-

pending occlusion was suspected from the sudden appearance of a typical anginal syndrome.

M. T., a male cutter, aged 45 years, was seen for the first time in March 1937. He complained of attacks of diarrhea, and an occasional stabbing pain in the region of the left nipple. The pain was not related to effort, meals, or excitement. It was mild and did not interfere with the patient's work. It usually persisted for several hours or days and was not relieved by nitroglycerin. The patient possessed an extremely emotional make-up. A complete physical examination revealed no abnor-

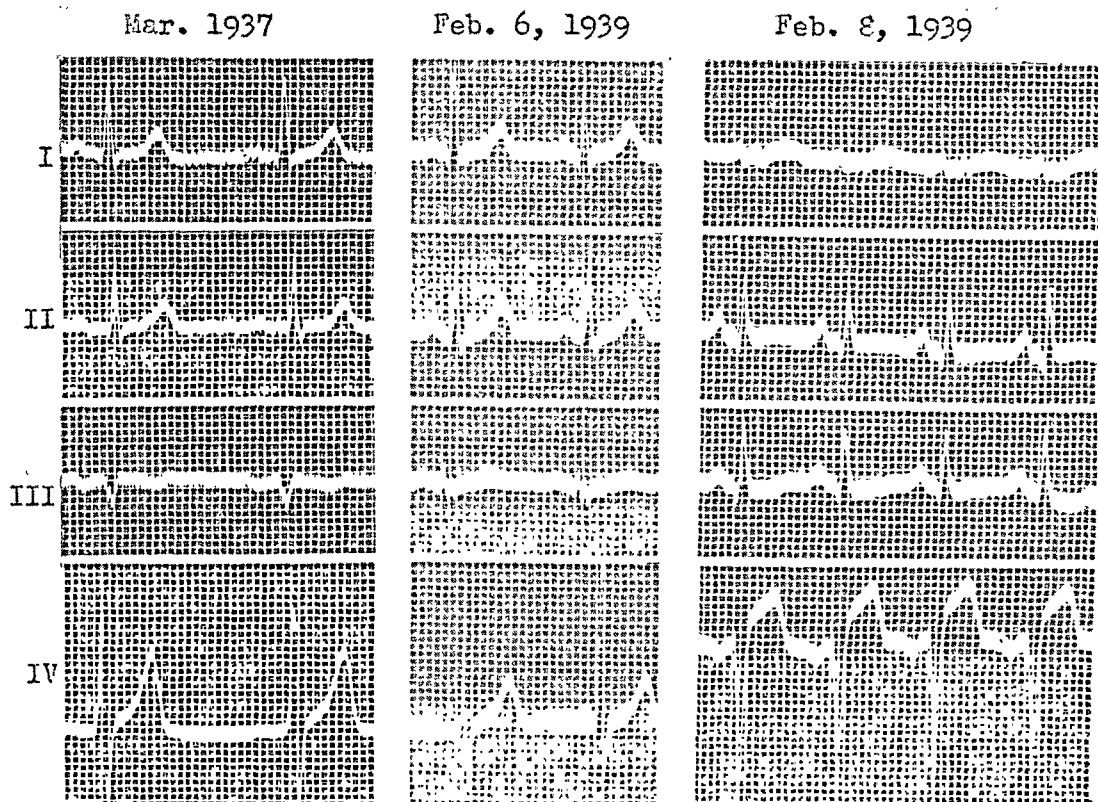


FIG. 1. M. T., Male, 45. Acute coronary occlusion, Feb. 7, 1939. Electrocardiograms during premonitory stage and after attack.

- A. March 1937. Two years before attack. Electrocardiogram is entirely normal.
- B. Feb. 6, 1939. Five days after onset of premonitory pain. Electrocardiogram is still normal. There is practically no change from previous record.
- C. Feb. 8, 1939. One day after attack. Electrocardiogram is now typical of acute anterior wall infarction. The QRS complex is W-shaped in Lead I and the initial positive deflection in Lead IV (R-4) is very small. The S-T transition is elevated in Leads I and IV and the T-waves are very low in the standard leads.

malities except for the presence of mucous colitis. The heart was not enlarged. The sounds were of good quality and there were no murmurs. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Fluoroscopy confirmed the normal size and shape of the heart. The electrocardiogram (figure 1A) was entirely normal.

In view of the negative cardiac findings and the fact that the precordial pain had none of the characteristics of an anginal syndrome due to disease of the coronary artery, the pain was considered to be extracardiac, and possibly of psychogenic origin. The mucous colitis also was attributable to psychic causes.

The symptoms persisted for two years without significant change, but the attacks of pain became milder and less frequent. During a two-weeks' sojourn in the country in January 1939, the pain ceased entirely, despite considerable walking. About two weeks after the patient's return, however, he began to notice a new kind of pain that occurred only when he walked. It was localized beneath the sternum and was of an oppressive character, which caused him to stop after walking half a block. On standing still, the pain stopped.

The patient was seen five days after the onset of this typical anginal syndrome, but examination revealed no departure from the normal findings of the previous two years. The electrocardiogram was unchanged (figure 1B). Nevertheless, we suspected that an occlusion of the coronary artery was in process of formation, and the patient was placed in bed. After a comfortable night, he was awakened by an excruciating substernal pain that required several injections of morphine before he felt relief. The syndrome was now typical of acute coronary occlusion, with a heart rate of 140 and gallop rhythm. On the following day the blood pressure had fallen to 90/70, and a pericardial friction rub was audible. The electrocardiogram presented the typical Q, T₁ pattern of anterior infarction (figure 1C).

GENERAL CONSIDERATIONS

It has been shown that in over two-fifths of our cases the onset of acute coronary occlusion was preceded by premonitory symptoms lasting for several hours, days, or even weeks. This suggests that the arterial occlusion develops gradually in a large proportion of cases, a view which is consistent with recent pathological studies¹⁴⁻¹⁶ concerning the mechanism of formation of coronary occlusion. These have demonstrated that the occlusion can form in three ways: Usually it is initiated by a hemorrhage into the intima of an arteriosclerotic plaque, with secondary thrombosis within the lumen as a result of injury or actual dissolution of the overlying endothelium. Less frequently there is a primary thrombosis on an arteriosclerotic plaque. In rare instances a hemorrhage into an atheromatous abscess (hematoma) closes the lumen without actual thrombosis.¹⁷ Careful examination of the site of occlusion has produced evidence^{10, 18} in some cases that the occlusion did not form suddenly but was produced by progressive or recurrent intramural hemorrhage or thrombosis. Thus, the hemorrhage within the plaque may show signs of organization while the thrombosis within the lumen may be of more recent appearance (figure 2); that is, the intramural hemorrhage may have occurred hours or days prior to the actual thrombosis. Again, the thrombus itself may not be uniform in appearance; its base adjacent to the plaque may show organization and fibroblastic formation, while the parietal portion may show a recent process.

On the basis of these observations it is possible to assume that the onset of the premonitory symptoms is associated with the rupture of a mural capillary, with hemorrhage, which suddenly narrows the lumen of the coronary artery but does not entirely block it. After a variable interval the lumen becomes completely obliterated as a result of the gradual formation of a secondary thrombus or of recurrent intimal hemorrhages, and it is only then that the acute symptoms appear. The process may take hours or days, and the

symptoms of complete occlusion may not occur for several weeks; during this period clinical evidence of coronary insufficiency is frequently observed, in the form of increasing angina pectoris.

A correlation of the factors often supposed to bring on the premonitory symptoms with the pathological observations presented above is also of interest. In previous reports^{18, 19, 20} we have presented evidence to prove that effort and excitement were not factors in the precipitation of acute coronary occlusion. It was shown that the percentage of attacks which occurred during sleep, rest, mild or routine activity, walking, moderate activity, or strenuous exertion, coincided with the percentage of the day spent by the ordinary person in these activities. This indicated that the circumstances preceding the attack were coincidental and that none of them was causally related to the coronary occlusion. The latter is the end result of an arteriosclerotic process and is entirely fortuitous. In this paper it has been shown that premonitory symptoms occurred during rest in over one-fourth of the cases, and during the mild or moderate activity or walking that is routine in daily life in the remaining three-fourths. But the symptoms were associated with strenuous effort in only two cases. Therefore, we believe that, as in the case of the complete occlusion, effort did not initiate the process resulting in premonitory symptoms. Were effort a factor, the incidence of strenuous exertion would be much greater than 2.9 per cent. It is our opinion that the premonitory pain results from a purely arteriosclerotic process, whose origin and progress are unrelated to physical activity or rest.

The association of premonitory symptoms with some activity in slightly over two-thirds of the cases can readily be explained on a physiological basis. During the process of thrombus formation, the blood-flow through the narrowed lumen of the coronary artery may be sufficient for the resting needs of the myocardium, but it is inadequate when the oxygen requirement of the heart is increased by activity. Therefore, premonitory pain is apt to appear with exertion, as in angina pectoris. This may account for the fact that premonitory symptoms did not occur in sleep. When complete occlusion occurs, however, the coronary flow is inadequate even at rest, and the sudden severe ischemia results in the characteristic onset of acute, prostrating pain usually at rest.

Differentiation of the attack of premonitory pain from actual arterial occlusion was often difficult, particularly when the pain was severe or persisted for several hours. In such cases it was also difficult to determine the exact time of onset of the clinical attack of coronary occlusion. Certain clinical observations made by Feil and Sampson and Eliaser, as well as by ourselves, however, are helpful in the recognition of premonitory pain. These authors showed that during the premonitory attack and until the onset of the arterial occlusion there usually were no clinical indications of complete occlusion or myocardial infarction. As a rule the patient was not confined to bed, and fever, leukocytosis, tachycardia, a drop in blood pressure, and other objective

evidences of myocardial infarction were lacking. In fact, after the initial attack of premonitory pain the patient was often symptom-free until the occlusion occurred. Furthermore, electrocardiograms taken during this period were usually normal, or showed no definite evidence of recent infarction.



FIG. 2. Medium power magnification of section through a recent coronary artery thrombosis secondary to dissolution of the intima of recurrent intimal hemorrhage. Fibrinoid transformation of the zone of hemorrhage within the intima (A) indicates an origin antedating the thrombosis within the lumen (B).

The patients in our series presented a similar clinical course. Many of them suffered only a single attack of premonitory pain and were then symptom-free for several hours or days. Others suffered repeated attacks of angina pectoris but were symptom-free in the intervals between attacks and remained ambulatory. On the other hand, a large group of patients suffered from persistent precordial discomfort or from progressive weakness, but presented no other symptom of acute occlusion. Electrocardiograms of three patients were obtained during the period of premonitory pain (figures 1, 3, and 4). It is seen that evidence of acute infarction is lacking in the initial record of each case despite the occurrence of precordial pain of several hours' duration. It is only in the later records taken following the onset of the occlusion as determined clinically, that the classical signs of infarction appear.

The absence of clinical or electrocardiographic signs of acute infarction during the stage of premonitory symptoms indicates that a gradually pro-

gressing coronary occlusion does not result in myocardial infarction until the occlusion is complete. However, during the partial occlusion coronary insufficiency is present, as demonstrated by the appearance of premonitory pain. It is thus difficult to explain the almost complete absence of acute electro-

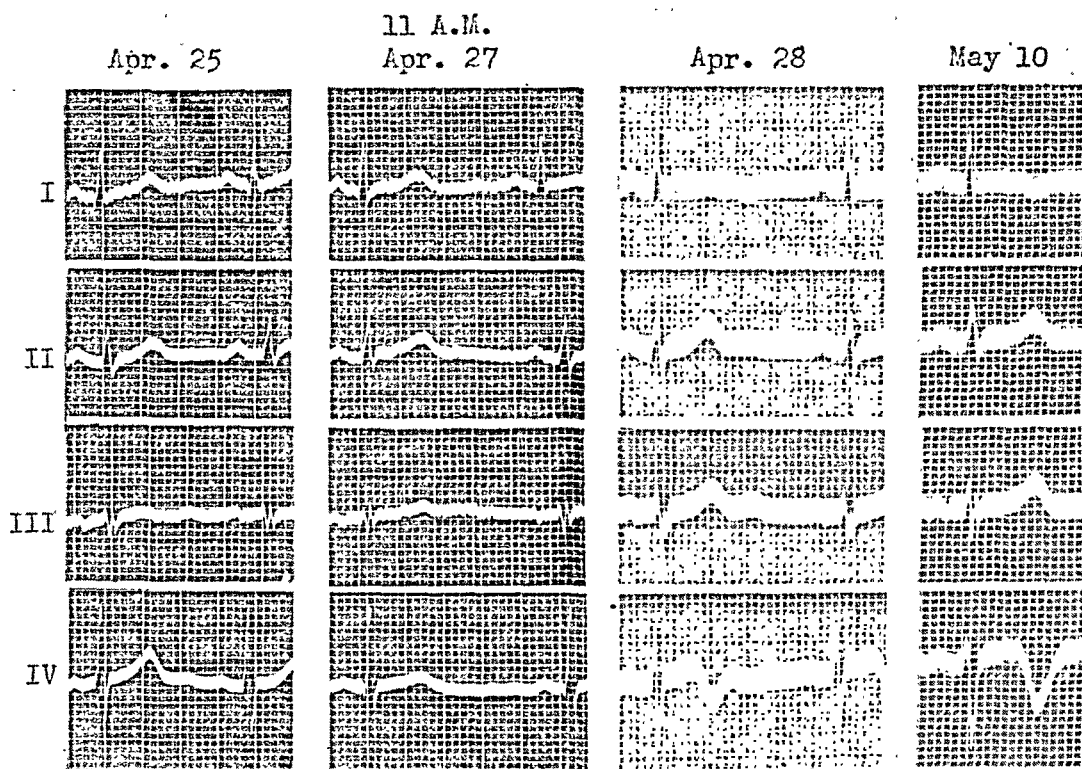


FIG. 3. N. G., Male, aged 55. Acute coronary occlusion April 27, 1939. Electrocardiograms during premonitory stage and following the attack.

- A. April 25, 1939. Slight pressure in chest six days ago while in movie. Awakened from sleep one day ago by precordial pressure, which was persistent. Electrocardiogram is entirely normal.
- B. April 27, 1939. 11 a.m. Persistent precordial pressure (premonitory pain). Electrocardiogram is still entirely normal. Severe attack of precordial and substernal pain occurred subsequently at 4 p.m.
- C. April 28, 1939. One day after attack. Electrocardiogram is now characteristic of anterior wall infarction. T_1 is low and semi-inverted, T_2 diphasic, and T_3 higher and upright.
- D. May 10, 1939. Two weeks after attack. Further progressive changes have occurred. T_1 is now inverted and coveplane. The initial positive deflection in Lead IV (R_4) is now very small.

cardiographic changes, since acute coronary insufficiency, by producing anoxic changes in the myocardium, often results in depression of the S-T transition and lowering of the T-waves. Lowering of the T-waves occurred in three of the cases reported by Feil, but we encountered none in our cases. One of the cases, however, presented slight depression of the S-T transition in Leads I and II (figure 4). It is possible that greater changes would appear if the electrocardiogram were taken during effort.

The possible recognition of an impending coronary occlusion by the

appearance of premonitory symptoms raises the question of whether the occlusion can be prevented by prompt bed rest. We believe that once the occlusion has commenced to form, its progression to complete obstruction of the coronary vessel cannot be prevented. In fact, we have been able to

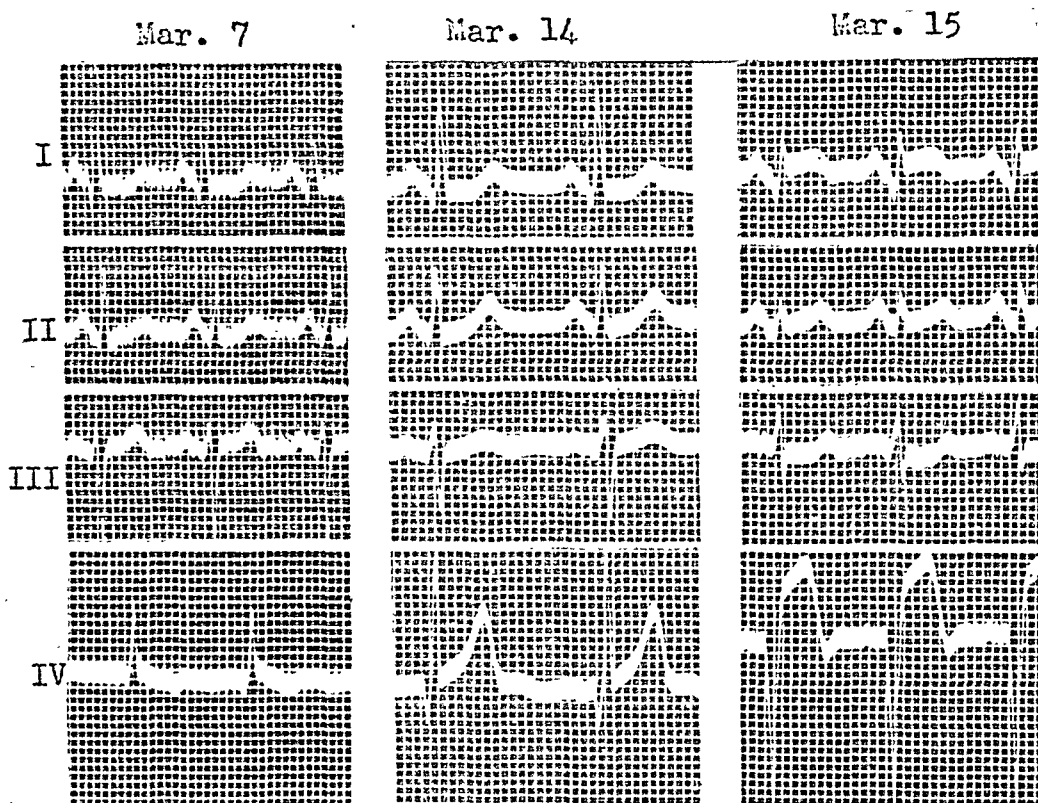


FIG. 4. L. E., Male, aged 50. Acute coronary occlusion, March 14, 1939. Electrocardiograms during premonitory stage and following attack.

- A. March 7, 1939. Typical angina pectoris on effort for three months. The electrocardiogram shows left axis deviation, small Q_1 , S-T depression in Lead I, and inverted T_1 . The changes are abnormal and indicate coronary artery disease.
- B. March 14, 1939. Persistent premonitory pain for one day. Record taken several hours before attack of occlusion. The Q_1 is larger, S-T transition is depressed in Leads I and II, T_1 is high and upright, and T_2 and T_3 higher. Although definite changes have occurred since the previous tracing, the record is not typical of acute infarction. The slight S-T depressions suggest coronary insufficiency.
- C. March, 15, 1939. Twelve hours following attack of coronary occlusion. The record is now characteristic of acute anterior wall infarction. Q_1 and Q_4 are deep, and the S-T transition is elevated in Leads I and IV, depressed in Lead III.

collect a group of 60 patients in whom occlusion occurred after they had been bed-ridden and at complete rest for weeks or months. Thirty of these patients are included in the present series, and six of them exhibited premonitory symptoms. The cases illustrated in figures 1, 3, and 4 also followed a typical clinical course to complete coronary occlusion despite immediate bed rest during the prodromal stage. However, placing the patient in bed immediately following the onset of premonitory symptoms may de-

crease the severity of the symptoms and of heart failure following complete occlusion, and thereby decrease the mortality rate. This point, as Sampson and Eliaser have stated, can be determined only by the study of a large series of cases in which a diagnosis of impending coronary occlusion is made and corroborated by subsequent events.

SUMMARY AND CONCLUSIONS

1. Premonitory symptoms were present in 44.2 per cent of 260 patients with acute coronary occlusion from whom detailed histories could be elicited.

2. In most cases the premonitory symptoms consisted of substernal or precordial pain or discomfort. Other prodromes were fatigue, weakness, gastric distress, dyspnea, palpitation, nervousness, and dizziness.

3. The sudden appearance of a typical anginal syndrome or the sudden acceleration of a previously existing anginal syndrome frequently preceded the attack of occlusion.

4. The premonitory symptoms usually appeared within 24 hours prior to the acute attack, but in some cases they began two or three weeks before.

5. The duration of symptoms varied from a few minutes to several hours. Although the premonitory pain was usually intermittent or continuous, a pain-free period frequently intervened before the onset of acute occlusion.

6. The onset of premonitory symptoms occurred during rest in 28.5 per cent of the cases, during mild or moderate activity or walking in 68.5 per cent, and during strenuous effort in 2.9 per cent.

7. The premonitory symptoms were not associated with clinical evidence of myocardial infarction. Fever, leukocytosis, tachycardia, drop in blood pressure, and characteristic electrocardiographic changes were absent. These factors are significant in differential diagnosis.

8. The anatomic basis for the premonitory symptoms is assumed to be a gradual occlusion of the lumen of the coronary artery by progressive or recurrent intramural hemorrhage or by primary thrombosis on a plaque, which may take hours or days for completion. The initiation and progression of coronary occlusion occurs irrespective of physical activity or lack of activity. However, the physiological coronary insufficiency and myocardial ischemia which ensue may result in precordial pain, which is often brought on or intensified by effort.

9. Early recognition of the premonitory symptoms should lead to a reduction of heart failure and decrease the mortality rate by means of immediate bed rest, which, however, will probably not prevent the impending occlusion.

REFERENCES

1. WEARN, J. T.: Thrombosis of the coronary arteries with infarction of the heart, *Am. Jr. Med. Sci.*, 1923, clxv, 250.
2. KAHN, M. H.: Prodromal symptoms in angina pectoris, *Am. Jr. Med. Sci.*, 1926, clxxii, 418.

3. PARKINSON, J., and BEDFORD, D. E.: Cardiac infarction and coronary thrombosis, *Lancet*, 1928, i, 4.
4. LEVY, R. L.: Diseases of the coronary arteries and cardiac pain, 1936, The MacMillan Company, New York.
5. LEVINE, S. A.: Clinical heart disease, 1936, W. B. Saunders, Philadelphia, p. 137.
6. BROUSTET, P.: Infarctus du myocarde à installation lente, *Arch. d. mal. du coeur*, 1937, xxx, 881.
7. WILLIUS, F. A.: Clinic on coronary thrombosis; symptoms attending the formation of a thrombus preceding complete coronary obstruction, *Proc. Staff Meet. Mayo Clin.*, 1937, xi, 414.
8. LEVINE, S. A.: Coronary thrombosis: its various clinical features, *Medicine*, 1929, viii, 245.
9. BEAN, W. B.: Infarction of the heart: symptomatology of the acute attack, *ANN. INT. MED.*, 1938, xi, 2086.
10. FEIL, H. I.: Preliminary pain in coronary thrombosis, *Am. Jr. Med. Sci.*, 1937, cxcii, 42.
11. SAMPSON, J. J., and ELIASER, M. J.: Diagnosis of impending acute coronary artery occlusion, *Am. Heart Jr.*, 1939, xiii, 675.
12. LANGSTON, W.: Premonitory pain in coronary artery occlusion, *South. Med. Jr.*, 1939, xxxii, 333.
13. MASTER, A. M., DACK, S., and JAFFE, H. J.: Activities associated with the onset of acute coronary artery occlusion, *Am. Heart Jr.*, 1939, xviii, 434.
14. PATERSON, J. C.: Vascularization and hemorrhage of intima of arteriosclerotic coronary arteries, *Arch. Path.*, 1936, xxii, 313.
15. WINTERNITZ, M. C., THOMAS, R. M., and LE COMPTE, P. M.: The biology of arteriosclerosis, 1938, Charles C. Thomas, Springfield, Ill.
16. HORN, H., and FINKELSTEIN, L.: Arteriosclerosis of the coronary arteries and the mechanism of their occlusion, *Am. Heart Jr.*, 1940, xix, 655.
17. WARTMAN, W. B.: Occlusion of coronary arteries by hemorrhage in their walls, *Am. Heart Jr.*, 1939, xv, 459.
18. PATERSON, J. C.: Relation of physical exertion and emotion to precipitation of coronary thrombosis, *Jr. Am. Med. Assoc.*, 1939, cxii, 895.
19. MASTER, A. M., DACK, S., and JAFFE, H. L.: Factors and events associated with the onset of coronary artery occlusion, *Jr. Am. Med. Assoc.*, 1937, cix, 546.
20. MASTER, A. M., DACK, S., and JAFFE, H. L.: The precipitating factors of coronary artery occlusion, *Indust. Med.*, 1939, viii, 327.

CLINICAL EXPERIMENTS WITH MIXTURES OF STANDARD AND PROTAMINE ZINC INSULINS*

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EVANESCENT action is one of the major disadvantages of standard insulin. Protamine zinc insulin overcomes this difficulty. Its absorption from the site of injection is slow; its therapeutic action is prolonged. But precisely because of its retarded action, short periods of post-prandial hyperglycemia and glycosuria are common with its use. If separate additional injections of standard insulin are given for the purpose of eliminating this objectionable feature, then one of the major advantages of protamine zinc insulin, a reduction in the number of injections, is partly or wholly lost.

Mixtures of the two forms of insulin in the same syringe have been given in attempts to retain the advantages of each. Campbell, Fletcher and Kerr¹ were "successful by using a long, narrow-bore syringe, and some care in avoiding mixing of the fluids, in giving the two insulins in a single syringe." Graham² used a similar method and emphasized that "It is important to prevent the possibility of mixing the two insulins in the bottles as the prolonged contact might cause a definite change." He attempted to avoid undue mixture by taking the protamine insulin first into the syringe and then the lighter "ordinary insulin remains in the upper part of the syringe" near the needle. Another method was suggested by a correspondent in a letter to the editor of the *Journal of the American Medical Association*.³ The writer stated that he gave a preliminary injection of standard insulin, removed the syringe from the needle, leaving the latter "sticking in the flesh," refilled the syringe with protamine zinc insulin, using another needle, and then, after removing the second needle from the syringe, injected the protamine zinc insulin through the first one left in situ. Campbell⁴ advised "using three-quarter inch needles and two syringes. A needle is attached to the syringe containing regular insulin, plunged far, but not deeply, under the skin and the contents injected; the needle is almost withdrawn, its direction changed, and again inserted to a point some distance from the original injection; the empty syringe is now removed, a syringe containing protamine zinc insulin substituted and its contents injected."

These complicated methods are hardly suitable for use by the patients themselves. Furthermore, the degree of intermingling of the two insulins, either in the syringe or in the tissues is highly uncertain. Unpredictable therapeutic results must be expected. It seemed to me better to insure thorough mixture before injection and to determine what proportion of one

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form of insulin to the other would be comparable in results to separate injections.

The use of mixtures is generally believed to fail for two stated reasons:

(1) Commercial solutions of protamine zinc insulin contain an excess of

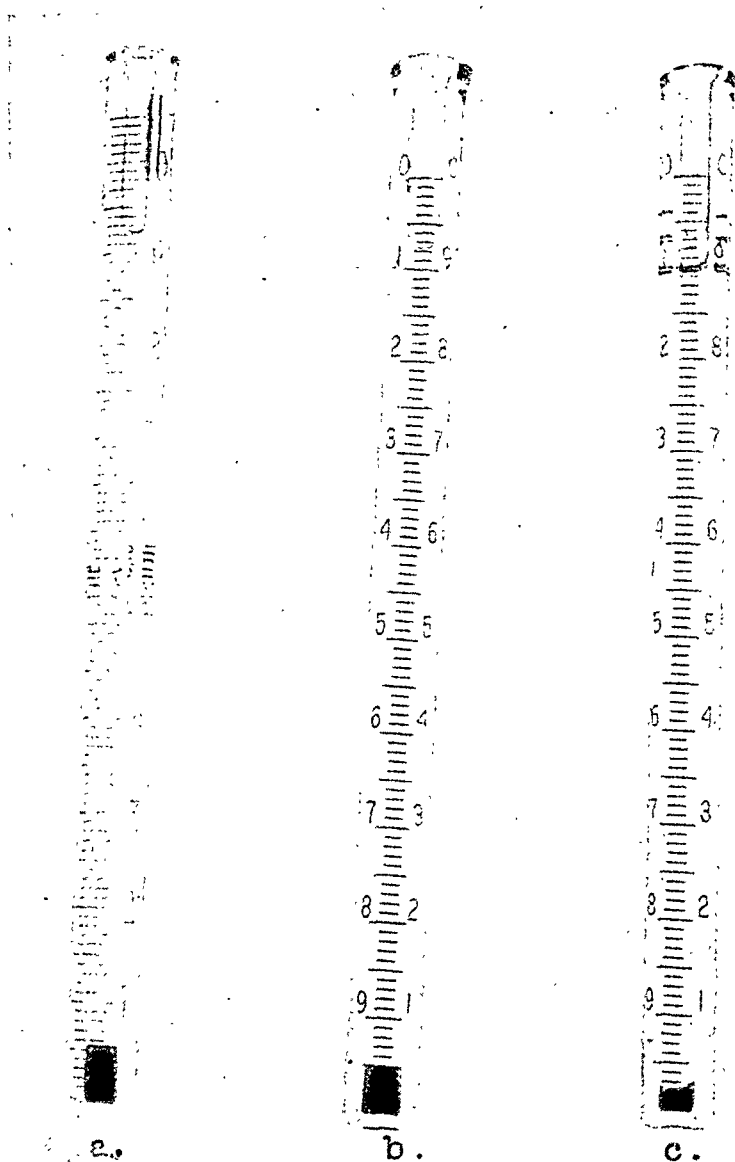


FIG. 1. Precipitate after centrifuging: (a) Solution of protamine zinc insulin U-40; (b) Mixture of equal parts of standard and protamine zinc insulin U-40; (c) Dilution of protamine zinc insulin U-40 with an equal amount of physiologic saline.

protamine; hence, added standard insulin will combine with the excess of protamine to form more protamine zinc insulin. (2) The activity of mixtures can not be predicted because of the uncertainty of the changes taking place in them. The first of these objections may be valid for certain pro-

portions in the mixtures, but the combining power of the excess protamine is not unlimited. By the addition of sufficiently large amounts of uncombined insulin a point is reached beyond which some of it may be expected to remain free. The clinical experiments to be reported show that the second objection applies not only to the mixtures but also to the use of separate injections.

According to Dr. F. B. Peck⁵ the protamine zinc insulin made by his company contains 1.25 mg. protamine per 100 units insulin, and the excess

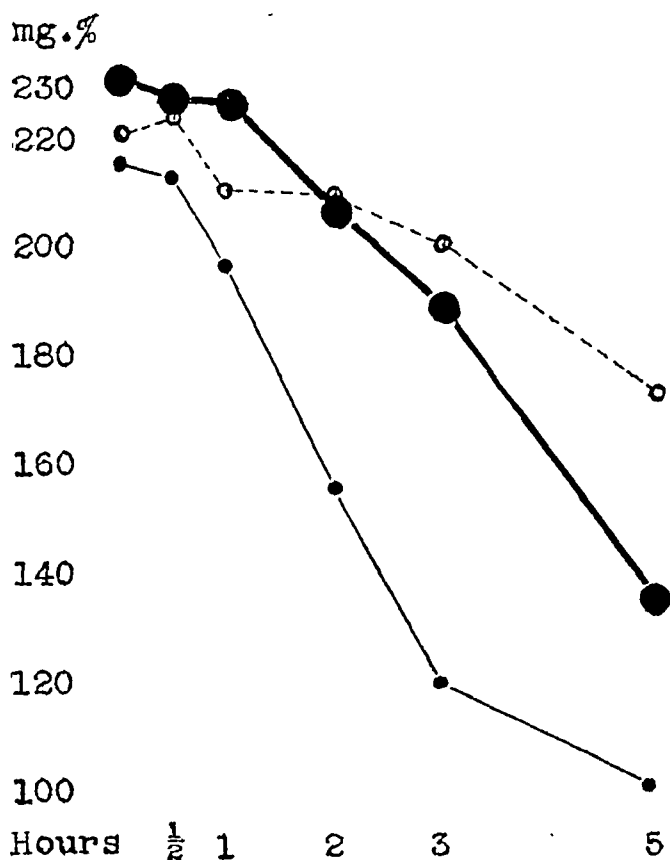


CHART 1. *Heavy line*: 1 c.c. (40 units) mixture A (equal parts standard and protamine zinc insulins). *Light line*: 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other. *Broken line*: 40 units protamine zinc insulin.

of protamine, although not uniform in all lots, is about 40 per cent. Mixtures of equal parts of standard insulin U-40 and protamine zinc insulin U-40, therefore, should contain 28 units protamine zinc insulin and 12 units uncombined insulin in each cubic centimeter, provided that the excess of protamine combines with a quantitatively proportional amount of the added free insulin. This, of course, is a highly speculative assumption. "The union of protamine and insulin," as Dr. W. R. Campbell⁶ has expressed it, "is not at all the simple one called to mind by the term 'protamine insulinate' but a very complex one."

Clinical experimentation was undertaken to determine if mixtures possess a reasonable degree of clinical predictability and usefulness despite their chemical uncertainty. To establish their practical value it must be shown that they have an early action greater than that of protamine zinc insulin and a prolonged action greater than that of standard insulin. Two sets of

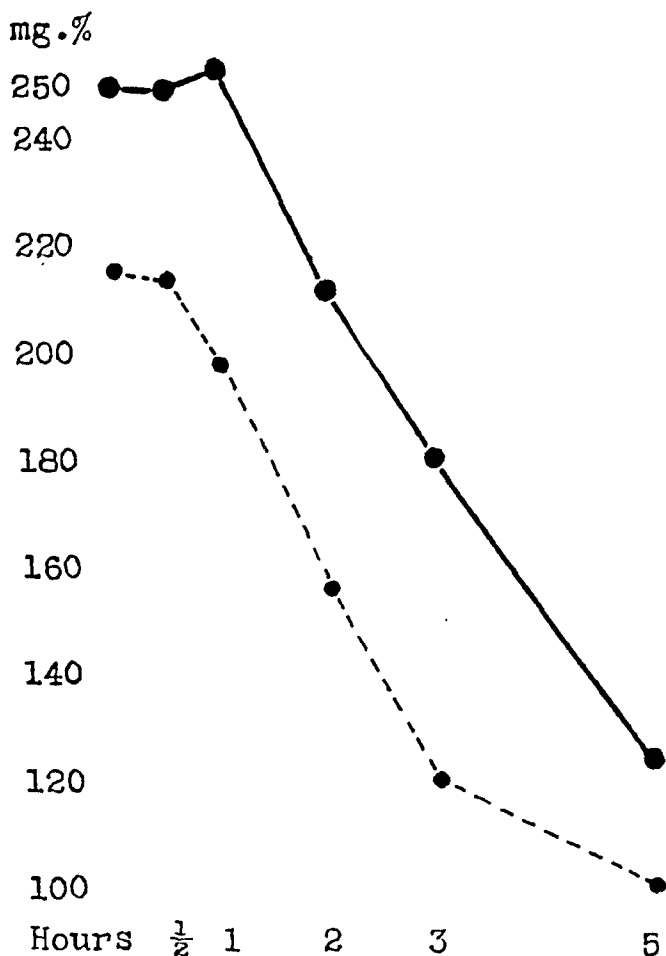


CHART 2. Solid line: 1 c.c. (40 units) mixture B (3 parts standard insulin, 2 parts protamine zinc insulin). Broken line: 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other.

experiments were planned for the purpose. The first consisted of estimations of the blood sugar before, and half an hour, one, three, and five hours after patients with diabetes had been injected with different mixtures of the two forms of insulin. The results were compared with those obtained after injections of protamine zinc insulin alone, and of 28 units protamine zinc insulin and 12 units uncombined insulin given in separate sites. The patients fasted after the evening meal of the previous day until the tests were completed. Ten tests were made on different patients with each method.

Comparison of the curves in chart 1, each representing the mean value of 10 tests, demonstrates that the immediate action of a mixture of equal parts of protamine zinc and standard insulin is less than that of the separate injections but greater than that of protamine zinc insulin alone. A mixture of three parts standard insulin and two parts protamine zinc insulin was then tried in an effort to get greater early action. The results obtained with this mixture, shown in chart 2, are roughly parallel to those produced by separate injections, although the latter appear to act somewhat more quickly.

To determine the predictability of action of the mixtures, two lots of the

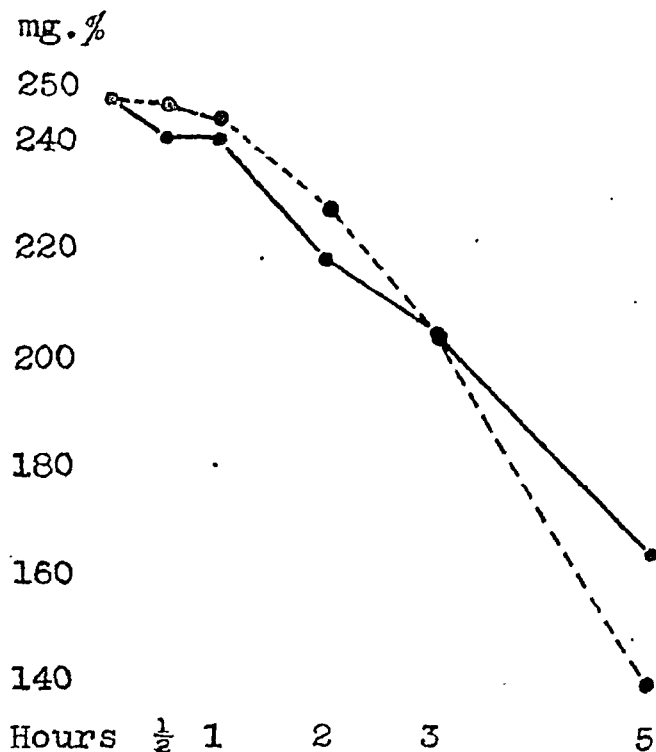
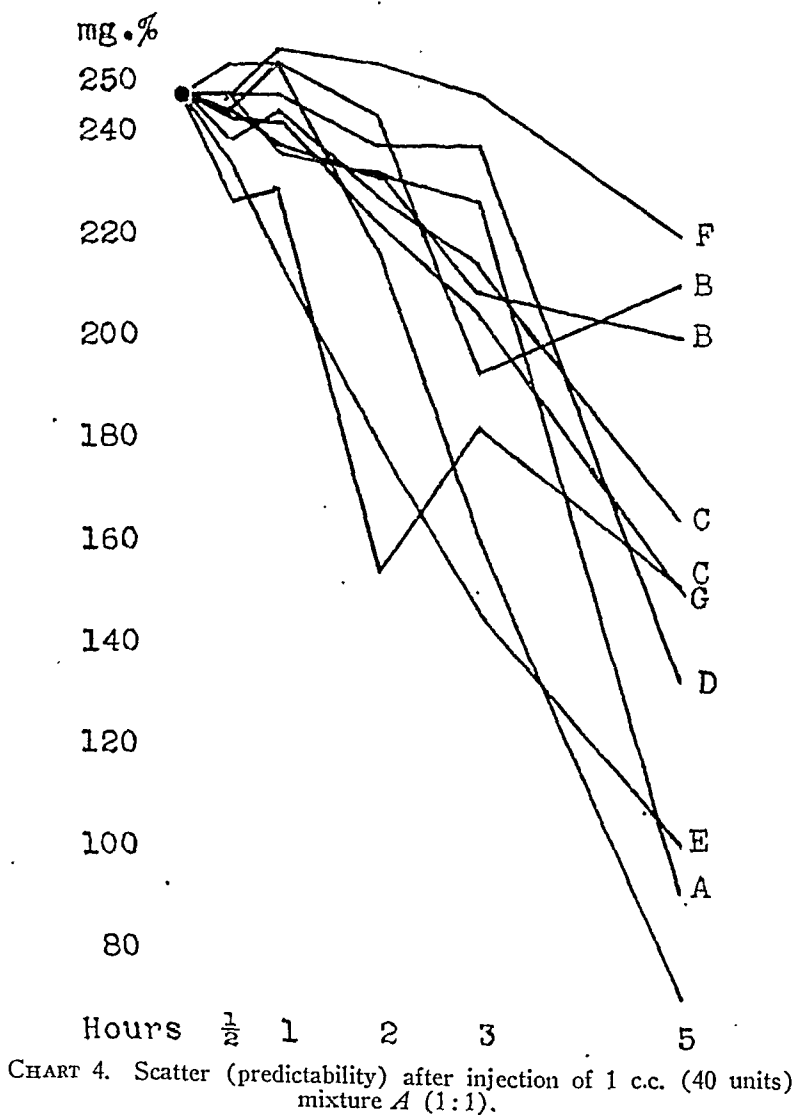


CHART 3. Comparison of results obtained with two lots of mixture A (equal parts standard and protamine zinc insulins) to show degree of predictability of action. Curves are arbitrarily started at the same initial level.

1:1 mixture, made from different vials of the two forms of insulin, were used, each for five of the 10 tests made with this mixture. By comparing the curves in chart 3, representing the mean values obtained in these two groups of five tests, it will be seen that the results are surprisingly similar. That is, a fair degree of predictability and uniformity of action of the mixtures is indicated. Another evidence of reasonable predictability of action is illustrated in charts 4, 5, and 6. In charts 4 and 6 the 10 individual curves obtained with the two experimental mixtures (1:1 and 3:2) are plotted separately (beginning at the same initial level), and the scatter (predictability) is compared with the spread of curves obtained with separate

injections of the two insulins (chart 5). Although there is a rather wide divergence in the responses in each group, the scatter is even greater with separate injections (chart 5) than it is with the mixtures (charts 4 and 6). In other words, predictability is at least as good with the mixtures as it is when the two forms of insulin are given separately. The difference in the responses in each group is probably the result of variation in the response



of different patients to insulin. This is substantiated by comparing the curves derived from experiments with the same patients and labeled with the same letters in charts 4 and 5. Patients A and E were very sensitive to insulin; patient B was much less so.

The results of this first set of experiments indicate that, with patients in the fasting state, appropriate mixtures of standard and protamine zinc

insulins have an immediate action similar to but slightly less rapid than that of separate injections, but much more pronounced than that of protamine zinc insulin alone; also, predictability of action is as good with the mixtures as it is with separate injections.

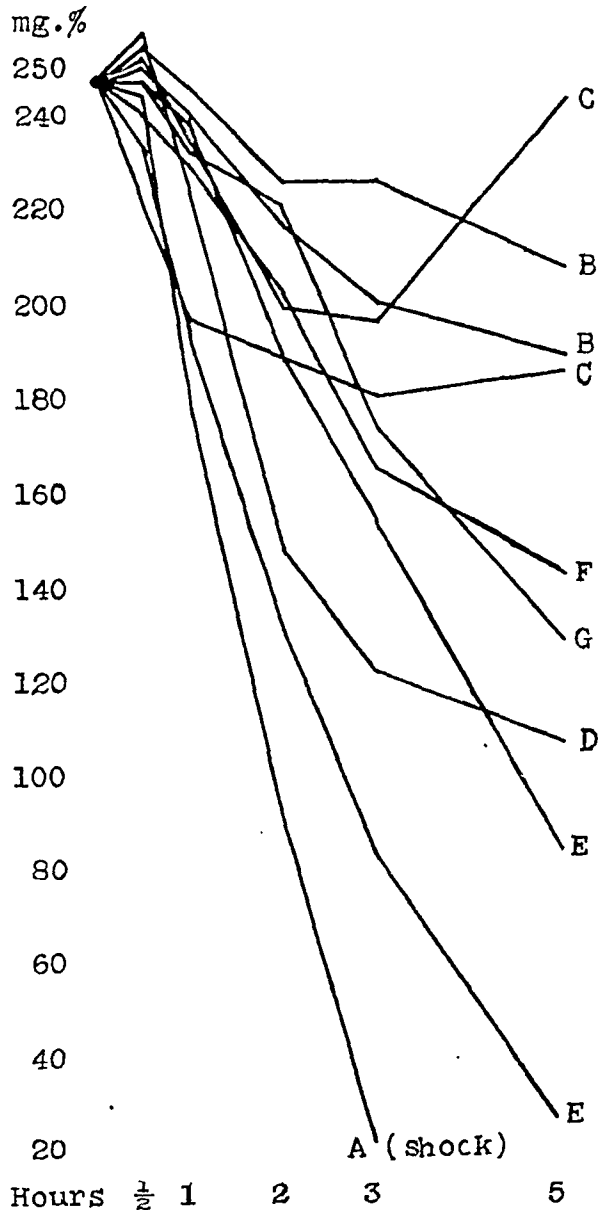


CHART 5. Scatter (predictability) after injection of 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other.

In the second phase of the study the degree of prolonged action, with patients taking food, was determined. For this purpose the insulin (always a total amount of 40 units, regardless of which method was used) was in-

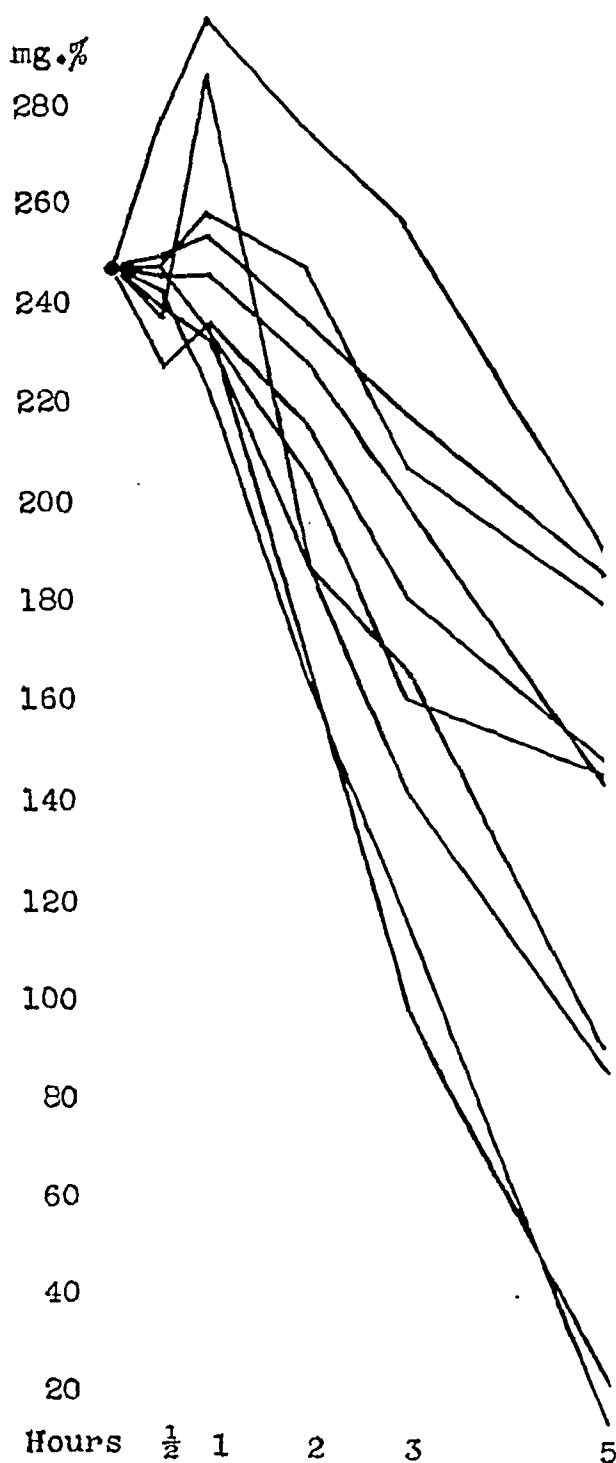


CHART 6. Scatter (predictability) after injection of 1 c.c. (40 units) mixture *B* (3 parts standard and 2 parts protamine zinc insulin).

jected at 7 a.m. Meals were given at 7:30 a.m., 12:30, and 5:30 p.m. Blood for examination was taken half an hour before and an hour after each meal, also at 10 p.m. and at 7 and 8:30 the following morning, with a second equal amount of insulin at 7 a.m. on that day. The intake of food at the four meals of the test periods was the same in all instances: breakfast, carbohydrate 41 gm., protein 10 gm., fat 23 gm., calories 411; dinner, carbohydrate 43 gm., protein 33 gm., fat 29 gm., calories 565; supper, carbohydrate 47 gm., protein 16 gm., fat 24 gm., calories 468.

The curves on charts 7 to 11, each of which represents the mean values obtained in 10 tests, illustrate the results that were obtained. With pro-

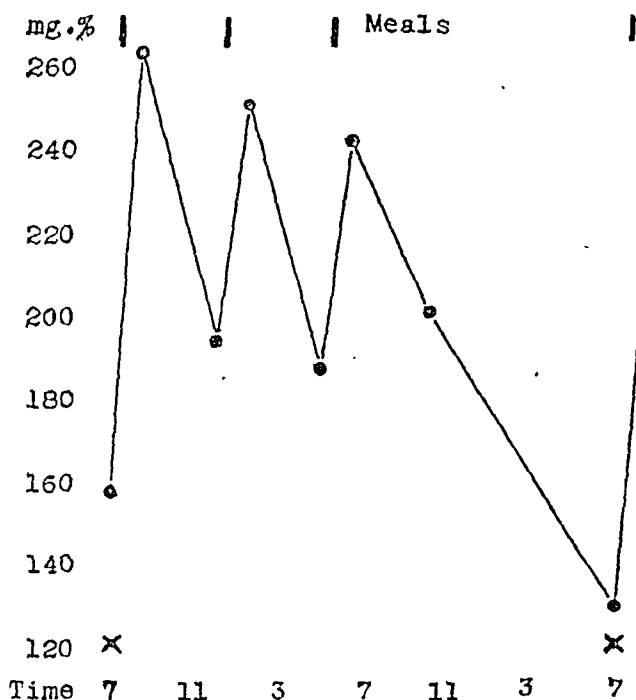


CHART 7. 40 units protamine zinc insulin at seven each morning (X).

tamine zinc insulin alone, marked and somewhat uniform hyperglycemia occurred after each meal. When the two insulins were given separately (28 units protamine zinc insulin in one arm, 12 units standard in the other), the rise after breakfast was largely avoided, but a high level of the blood sugar occurred toward evening, evidently because the standard insulin had spent itself at that time, and the protamine zinc insulin had not yet reached the period of its greatest activity. Increasing the amount of either would not be safe; with a larger dose of standard insulin hypoglycemia might occur before noon, with more protamine zinc insulin the dangerous time would come in the early hours of the morning.

Results with the mixtures were less promising under the conditions of this part of the study than they were with fasting patients. The hyper-

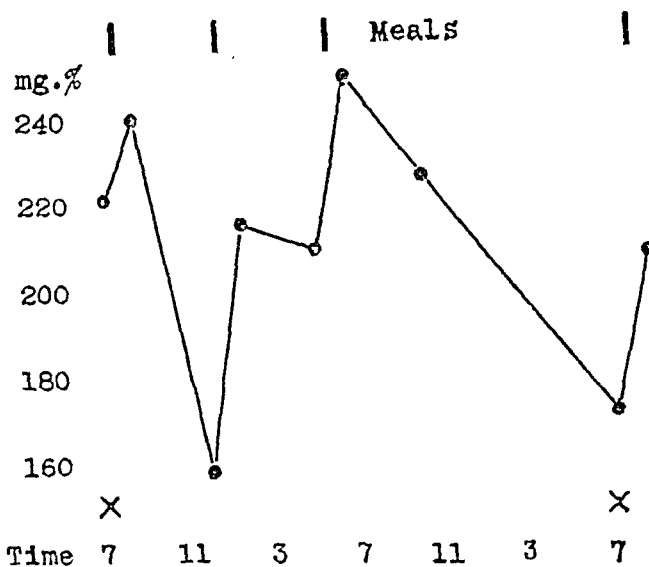


CHART 8. 28 units protamine zinc insulin in one arm, 12 units standard insulin in the other, at seven each morning (X).

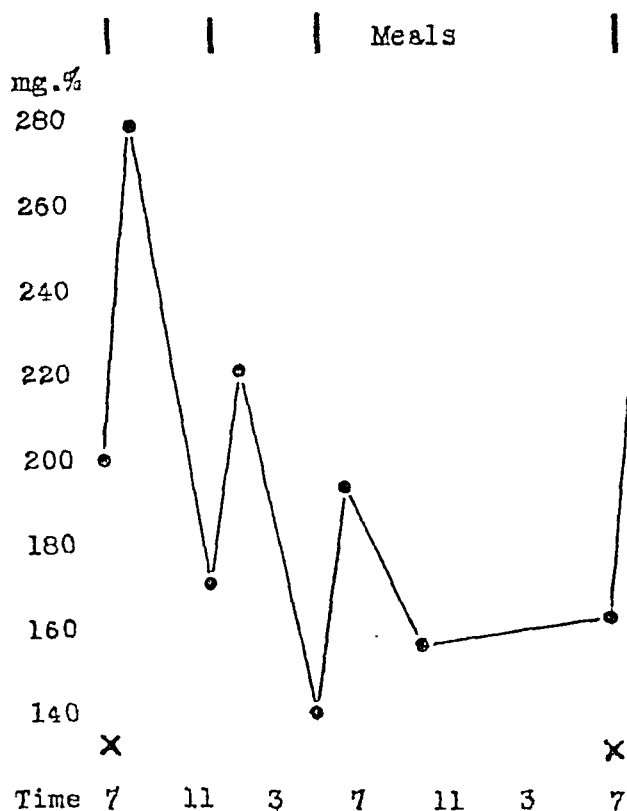


CHART 9. 1 c.c. (40 units) mixture B (3 parts standard insulin, 2 parts protamine zinc insulin) at seven each morning (X).

glycemia after breakfast was less well controlled than it was with separate injections, although it was slightly less marked than that occurring with protamine zinc insulin alone. Mixture B, consisting of three parts standard and two parts protamine zinc insulin, gave the most encouraging results, with a slightly smaller elevation of the blood sugar after meals and, after the initial rise in the morning, a somewhat more uniform level of glycemia throughout the day. Increasing the proportion of standard insulin in the

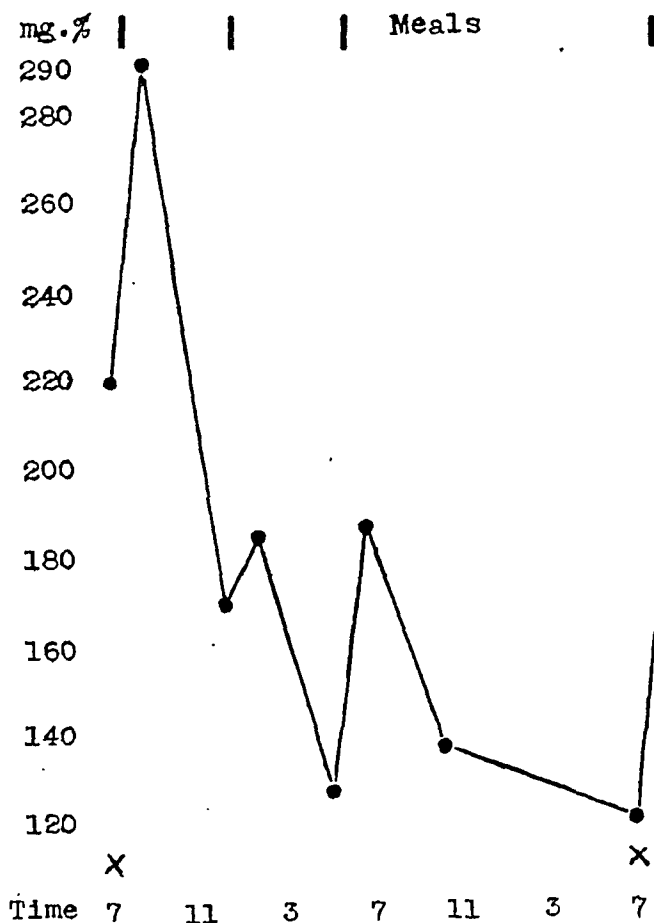


CHART 10. 1 c.c. (40 units) mixture C (2 parts standard insulin, 1 part protamine zinc insulin) at seven each morning (X).

mixtures, contrary to expectation, had only a slight effect in lessening the degree of hyperglycemia occurring immediately after breakfast, although the initial rise was followed very quickly by a marked depression of the blood sugar before noon. This was especially noticed in experiments with mixture D, consisting of three parts standard insulin and one part protamine zinc insulin (chart 11), in which the mean level of glycemia in the 10 cases of this group declined from 338 mg. to 128 mg. within three and a half hours.. This remarkable result seemed to indicate that the uncombined

portion of insulin in the mixture, although present in a relatively large amount, did not act as quickly as the standard insulin that was injected separately; but its action was much prompter than that of protamine zinc insulin. Attention has previously been called to the similar but less pro-

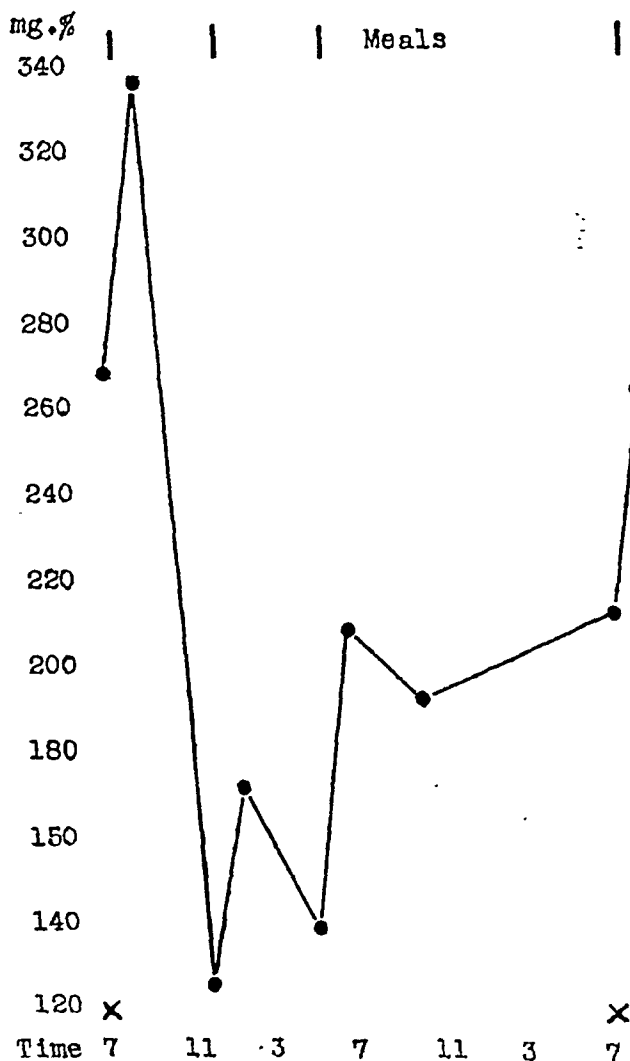


CHART 11. 1 c.c. (40 units) mixture *D* (3 parts standard insulin, 1 part protamine zinc insulin) at seven each morning (X).

nounced results obtained in the experiments with fasting patients (charts 1 and 2).

In an endeavor to find an explanation of this phenomenon, some of the mixture was centrifuged, and the clear supernate was injected in a patient with diabetes who was particularly sensitive to insulin (curves A in charts 4 and 5). As indicated in chart 12, the clear supernatant fluid did not contain insulin at all. All of the added standard insulin had apparently

been precipitated. This is confirmed by the fact that centrifuging equal amounts of 1:1 mixture and of plain solution of protamine zinc insulin yielded equal amounts of precipitate, whereas a comparable dilution with water or physiologic saline yielded only about half as much (figure 1). Yet the clinical results obtained with various mixtures (illustrated in charts 9, 10, and 11) differed materially from those obtained with protamine zinc insulin alone (chart 7). The immediate response with the former was much greater and indicated that much of the added standard insulin had not combined, at least not firmly, with protamine, but was present in a more readily available form.

The explanation is to be found in changes in the hydrogen ion concentration. Standard solutions of insulin are strongly acid in reaction (pH 2.5-4), whereas solutions of protamine zinc insulin have a pH of 7-8. In

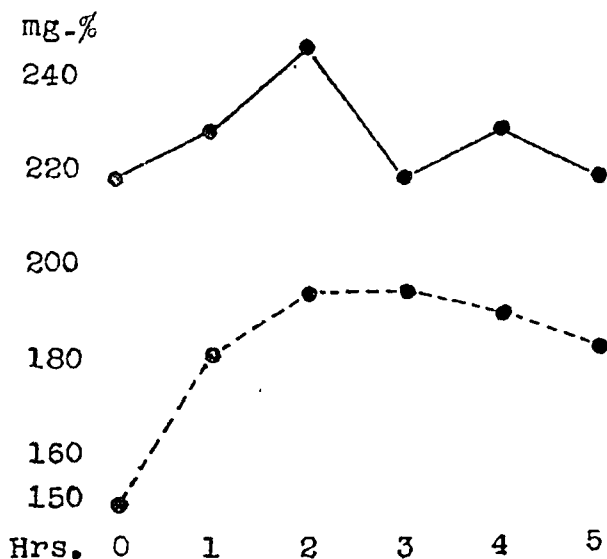


CHART 12. Curves showing absence of action of supernatant fluid obtained after centrifuging mixture *B* (broken line) and mixture *C* (solid line), in a patient who was particularly sensitive to insulin (Curves *A* in charts 4 and 5).

the mixtures the protamine apparently acts as a buffer, because in mixtures of equal parts of the two forms of insulin the hydrogen ion concentration is not half way between those of the constituents but nearer that of protamine zinc insulin. The degree of acidity increased somewhat with the amount of standard insulin in the mixtures.

The isoelectric point of insulin is about pH 5, so that at or near this level of hydrogen ion concentration it is precipitated. A study of charts 7 to 11 shows that the precipitated insulin, although not combined with protamine, had a slightly slower action than insulin in solution, but its action was much more rapid than that of protamine zinc insulin.

As a result of this finding, another experiment was carried out in which the standard solution of insulin was alkalinized to a reaction approximately

equal to that of the protamine zinc insulin before the two solutions were mixed. It was done by adding 0.12 c.c. of twentieth normal solution of sodium hydroxide to 5 c.c. of standard insulin. During the addition of the alkali a precipitate was formed which redissolved when the whole amount of alkali had been added. Clinical results with the alkalinized mixtures were not better than those obtained with the plain combinations, and there was some evidence that they deteriorated with time. Further study in this direction, therefore, was abandoned.

SUMMARY

Experiments are recorded which indicate that mixtures of standard and protamine zinc insulin are suitable for clinical use. The claim that the results with such mixtures are wholly unpredictable is not supported by these experiments. Predictability is at least as good as it is with separate injections of the two forms of insulin. A mixture of three parts of standard insulin and two parts of protamine zinc insulin gave the most promising results. The use of such a mixture may be advantageous in the treatment of certain suitable patients who require injections of standard insulin as a supplement to treatment with protamine zinc insulin. Moreover, they may be preferable to the use of protamine zinc insulin alone when it does not prevent marked post-prandial periods of hyperglycemia.

BIBLIOGRAPHY

1. CAMPBELL, W. R., FLETCHER, A. A., and KERR, R. B.: Protamine insulin in the treatment of diabetes mellitus, *Am. Jr. Med. Sci.*, 1936, cxcii, 589.
2. GRAHAM, G.: The use of a mixture of ordinary and protamine insulin, *Acta med. Scand.* (Supplement), 1938, xc, 54.
3. Queries and Minor Notes, *Jr. Am. Med. Assoc.*, 1939, cxii, 871.
4. CAMPBELL, W. R.: Some difficulties in the use of the insulins in diabetic practice, *Bull. New York Acad. Med.*, 1939, xv, 579.
5. PECK, F. B.: Personal communication.
6. CAMPBELL, W. R.: Personal communication.

SUBACUTE STAPHYLOCOCCUS ENDOCARDITIS AND STAPHYLOCOCCUS BACTEREMIA WITHOUT ENDOCARDITIS WITH A REPORT OF THE FAVORABLE EFFECT OF SULFANILAMIDE AND SULFATHIAZOLE IN TWO CASES *

By HAMILTON SOUTHWORTH, M.D., *New York, N. Y.*

THE staphylococcus is not an uncommon invader of the human blood stream but cases of prolonged bacteremia without an obvious focus of infection are rare. In most instances an obvious portal of entry is present and the bacteremia is either a temporary one at the height of the local infection or a septicemia with a stormy course. Low-grade bacteremias of long duration do, however, occur, and in such cases the question of a subacute or chronic endocarditis is invariably raised.

Searching for such case reports, with or without endocarditis, in the literature, we were able to find only those that have been listed in table 1.^{1, 2, 3, 4, 5, 6} All cases in which there was a proved focus (osteomyelitis,

TABLE I

Author	Organism	Endocarditis at Autopsy	Clinical Duration	First Positive Culture
Thayer	<i>Staph. aureus</i>	+	5-6 months	No culture taken
Stich	<i>Staph. albus</i>	+	5½ months	About 4 wks. before death
Le Clerc	<i>Staph. albus</i>	No autopsy	8-9 months	2 months before death
Young	<i>Staph. albus</i>	No autopsy	11 months	10 months before death
Lemierre et al.	<i>Staph. aureus</i>	+	14 months	2 months before death
Horder	<i>Staph. albus</i>	+	24-30 months	—

urinary tract infection, etc.) have been excluded,† as well as those which lacked evidence, at least of a clinical nature, that the bacteremia was of over five months' duration.

It is to be noted that all these cases presumably had endocarditis. All of the cases ended fatally, and in each of the four instances in which autopsy was performed an intracardiac vegetation was found. In four the staphylococcus involved was described as an albus and in two as an aureus. No further bacteriologic study was made. In only one instance was the organism obtained from the blood stream more than two months before death.

To this list we would like to add two cases from the Presbyterian Hospital in New York City.

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From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and The Presbyterian Hospital, New York City.

† Horder's case has been included even though there is no mention whether or not there was a focus other than on the heart valves.

Case 1. R. M., a 33-year-old social worker, was first admitted to the Presbyterian Hospital in March 1937. At the age of nine she was told she had congenital heart disease. In September 1935 she had been admitted to another hospital with a history of four days of pleurisy which was confirmed by roentgen-ray. In addition to the signs of a congenital heart lesion, two petechiae were noticed, and a *Staphylococcus aureus* was obtained from the blood stream. Her fever subsided and she was able to return to work. But in November 1935 an abscess of the buttock necessitated readmission and this was followed by a recurrence of pain in the chest and of fever and then by an abscess near the other hip. In March 1936 she became aware of nightly fever (101° – 102°), cough, night-sweats, and a weight loss of 12 pounds. In October 1936 she was again admitted with an acute pulmonary infection and repeated blood cultures grew out a *Staphylococcus aureus*. The diagnosis of bacterial endocarditis was made. In December 1936 she spent four weeks in another hospital because of fever, sweats and cough. The diagnosis of subacute bacterial endocarditis was thought probable, though blood cultures remained negative.

On admission to the Presbyterian Hospital the patient had an enlarged heart with signs typical of a patent ductus arteriosus. The spleen extended 2 cm. below the costal margin but no petechiae were observed. It was noted that she looked tired rather than seriously ill. Her hemoglobin was 79 per cent, red blood cells 3,800,000, white blood cells 7,600, and differential count normal. The sedimentation rate (Westgren) was 76 mm./1 hour. Urinalysis was normal; the blood Wassermann test was negative. Five successive blood cultures each grew out a *Staphylococcus albus*. This was studied by Dr. Richard Thompson and found to be a typical Group C non-pathogen, mannitol and coagulase negative.⁶ A thorough search for a focus of infection (which included roentgen-rays of sinuses, mastoids, teeth, lungs, and skeleton; cultures of urine and of irrigations of antra and sphenoid; and gall-bladder and gastrointestinal series) was entirely fruitless. The patient showed fever only intermittently.

She was placed on sulfanilamide, receiving 3.6 gm. daily for two weeks and attaining a blood level of 4 mg. per cent of the free drug. Thereafter five blood cultures all remained sterile and she went home symptom-free, the consensus of medical opinion being that she had had a bacteremia without endocarditis.

Three months later, however, fever recurred and staphylococci were again obtained by blood culture. The patient was readmitted for more sulfanilamide but developed fever and rash so that the drug had to be stopped after four days without therapeutic effect. Cardiac insufficiency then set in with a rise in venous pressure to 180 mm. of saline, and in spite of treatment the patient died in September 1937, a death of cardiac failure, not of sepsis.

Autopsy, unfortunately limited to the heart and lungs, revealed no endocarditis and no origin for the bacteremia. The heart was slightly enlarged, a patent ductus arteriosus was present, and there was evidence of chronic passive congestion.

Case 2. M. B., a 70-year-old secretary, was admitted in November 1938. Twenty-five years previously he had been told he had an organic heart murmur but he remembered no symptoms suggestive of rheumatic fever. In May 1938 he first became ill with fever, malaise, and night-sweats. Shortly thereafter he developed tender, red, painful areas successively in the neck, the hip, both arms, and finally in the fingers and toes. All of these were of brief duration and subsided without supuration. In September 1938 he was in the Johns Hopkins Hospital under the care of Dr. Louis Hamburger. A probable diagnosis of subacute bacterial endocarditis was made, but by blood culture nothing was obtained save a *Staphylococcus albus* which appeared only once on a plate and once in a flask and was therefore considered a contaminant. During the next two months the patient was able to work part time and fever occurred only intermittently in association with recurrences of what appeared to be metastatic infective foci, usually in the extremities.

On admission the patient was chronically but not severely ill. The heart seemed slightly enlarged and there was a systolic murmur of moderate intensity at the apex. The liver edge extended 3 cm. below the costal margin and a firm splenic tip was just palpable. Hemoglobin was 11.2 gm. (77 per cent), red blood cells 4,030,000, white blood cells 10,250 with 81 per cent polymorphonuclear leukocytes. Urinalysis was negative. The sedimentation rate (Westgren) was 52 mm./1 hour. Two blood cultures grew out *Staphylococcus albus* in both flasks. A thorough search for a focus of infection (roentgen-rays of teeth, lungs, genito-urinary tract, gastrointestinal tract and gall-bladder) proved negative. The patient refused chemotherapy and went home with a probable diagnosis of subacute staphylococcal endocarditis. Dr. Richard Thompson studied the organism and found it to give a lemon growth, to be antigenically a group C, but to show evidences of pathogenicity in that it fermented mannitol and produced coagulase.⁶

During the next year the patient continued at intervals to run fever to 101° or 102°. At first these febrile episodes were nearly always accompanied by the development of a non-suppurating peripheral area of infection; later the fever occurred more frequently without obvious metastatic focus. Between bouts the patient felt well and carried on his usual work. In fact, after a period of low morale in February 1939, he even gained in weight. No petechiae were observed and the spleen did not increase in size. It was noticeable, however, that the systolic murmur grew progressively louder and this in spite of the fact that there was no increase in anemia. In October 1939 blood cultures taken during an afebrile interlude, again grew out a *Staphylococcus albus* in both flasks.

In January 1940 a supply of sulfathiazole was obtained through the kindness of Dr. George Harrop of E. R. Squibb and Sons, and the patient consented to take it. It was then found that the patient had gained 15 pounds in 14 months and that his hemoglobin had risen to 14.0 gm. (98 per cent) with 4,850,000 red blood cells and 6,850 white blood cells and a normal differential count. But on blood culture *Staphylococcus albus* was still obtained and the sedimentation rate was 59 mm./1 hour. Sulfathiazole was then begun in increasing doses until a blood level of 13.5 mg. of free and 16.0 of total drug was obtained. In 10 days a total of 41.25 gm. was administered. At the end of this time fever, a macular rash, and a sudden drop in the percentage of granulocytes to 39 per cent with the appearance of 3 per cent of myelocytes caused its discontinuance. In seven days all of these findings had disappeared. The hemoglobin fell gradually from 14.0 to 12.8 gm. but the total leukocytes did not vary significantly. The only urinary changes occurred during the week after the sulfathiazole was stopped and consisted of a transitory faint trace of albumin and a rare red blood cell and hyaline cast in the centrifuged sediment.

After 10 grams of sulfathiazole had been administered, blood cultures, for the first time in 17 months, remained sterile. At the end of the course of chemotherapy and one week later there was still no growth. Since that time 12 months have elapsed and the patient has been entirely free of fever and metastatic infection. He has continued to gain in strength and weight. Two more blood cultures have remained sterile. The heart murmur has increased slightly but the spleen has receded until it is no longer palpable. The sedimentation rate on January 14, 1941, had fallen to 7 mm./hour.

The two cases here reported illustrate the extreme difficulty of differentiating without an autopsy subacute endocarditis from subacute bacteremia without endocarditis when caused by the staphylococcus, unless an unmistakable change occurs in a heart murmur without the development of anemia. This difficulty is increased by two factors. First, staphylococcus bacteremia is well known for its ability to cause metastatic abscesses and splenomegaly.

And second, as pointed out by Thayer,⁸ only about 20 per cent of staphylococcus endocarditis cases ever have petechial hemorrhages.

In both of our cases, endocarditis was suspected. The first, with its congenital anomaly, the recurrence of bacteremia after chemotherapy, the story of petechiae at another hospital, and the unexplained rapidity of the terminal cardiac insufficiency, was certainly very suggestive, and yet, at autopsy, no vegetations were found. In the second case the increase in the heart murmur and the initially painful fingers and toes suggested endocarditis, but the exceedingly low-grade course and the effectiveness to date of chemotherapy may be evidence against it.

SUMMARY

1. Two cases are reported of prolonged (over five months) staphylococcus bacteremia without an obvious focus of infection other than possibly an endocarditis. Six similar instances have been gathered from the literature.

2. In one case staphylococci were consistently present in the blood stream for 17 months and yet the patient maintained relatively good health.

3. In both cases the staphylococcus was antigenically a group C organism.

4. The difficulty of determining without autopsy whether or not there really is an endocarditis is stressed.

5. The favorable influence in one case of sulfanilamide and in another of sulfathiazole is described.

REFERENCES

1. THAYER, W. S.: Studies on bacterial (infective) endocarditis, Johns Hopkins Hosp. Rep., 1926, xxii, 1.
2. STICH, B.: Subacute bacterial endocarditis due to *Staphylococcus albus*, Arch. Int. Med., 1932, xlix, 666.
3. LECLERC, F.: L'Endocardite infectieuse a évolution lente et prolonguée, Lyon Med., 1906, cvii, 1017.
4. YOUNG, C. J.: Pregnancy at term complicated by *Staphylococcus albus* septicemia and cerebral hemorrhage, Ohio State Med. Jr., 1936, xxxii, 24.
5. LEMIERRE, A., LAPORTE, A., and BOTTANSKI, E.: Endocarditis vegetantes a staphylocoque, Bull. et mém. Soc. med. d. hôp. de Paris, 1931, xlvii, 532.
6. HORDER, T. J.: Infective endocarditis, Quart. Jr. Med., 1908-9, ii, 289-324.
7. THOMPSON, R., and CHORAZO, D.: Correlated antigenic and biochemical properties of staphylococci, Jr. Bact., 1937, xxxiv, 69-79.
8. THAYER, W. S.: Bacterial or infective endocarditis, Edinburgh Med. Jr., 1931, xxxviii, 237-265, 307-334.

TREATMENT OF PNEUMOCOCCIC PNEUMONIAS WITH SULFAPYRIDINE, SULFATHIAZOLE AND SERUM; ANALYSIS OF THE RESULTS OF SPECIFIC THERAPY AT THE BOSTON CITY HOSPITAL FROM JULY 1939 THROUGH JUNE 1940 *

By MAXWELL FINLAND, M.D., F.A.C.P., FRANCIS C. LOWELL, M.D., and
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THE present report deals with the results of specific therapy in the pneumococcic pneumonias of adults at the Boston City Hospital during the second year in which effective chemicals were available. In the preceding year,¹ specific serums and sulfapyridine each were used separately in a large proportion of the cases, and the results of treatment with each of these agents were quite comparable. The combination of serum and sulfapyridine was used during that year in some of the most severe cases, while a considerable proportion of the cases received neither of these remedies. During the year covered in the present report (July 1939 through June 1940), sulfapyridine therapy was started, in general, as soon as the diagnosis of pneumonia was made, and serum was given, in addition, to some of the most severe cases and to those in whom the drug either occasioned excessive discomfort or failed to bring about an adequate clinical response. Beginning February 1, sulfathiazole was substituted for sulfapyridine and used in identically the same manner on four of 12 medical wards. As in previous studies, all cases with clinical, roentgenographic or autopsy findings of pneumonia associated with the identification of pneumococci are included for analysis. The proportion of patients who failed to receive any specific treatment was much smaller than in the previous year.

ANALYSIS OF CASES AND RESULTS OF THERAPY

The distribution of cases according to the type of pneumococcus and the kind of specific therapy used is shown in table 1. Of the 911 cases, 691, or 76 per cent, were treated with either sulfapyridine, sulfathiazole or serum, or with a combination of serum and one of the two drugs. Among these 691 specifically treated cases there were 113 deaths, a mortality of 16.4 per cent. In the previous year, only 54 per cent of all the pneumococcic pneumonias received sulfapyridine or serum, or both, and the mortality among the cases so treated was 17.5 per cent. During the present year, serum was used, for the most part, to supplement drug therapy in some of the severe cases due to the common Types I, II, V, VII and VIII. More than one-

* Received for publication August 31, 1940.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

TABLE I

Distribution of Cases and Deaths According to Pneumococcus Types
Boston City Hospital, July 1, 1939-June 30, 1940

Type	Sulfapyridine		Sulfathiazole		Sulfapyridine and Serum		Sulfathiazole and Serum		No Specific Therapy		All Cases	
	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died§	No.	Died
I	71 ¹⁶	6 ⁴	26 ⁵	1 ¹	28 ¹¹	4 ³	8 ³	1 ¹	11 ³	4 ³ (4)	147 ^{38*}	16 ¹²
II	32 ⁷	3 ²	9 ²	1	19 ⁹	3 ³	2 ²	0	4	2 (2)	66 ²⁰	9 ³
III	73 ¹⁰	19 ⁸	14	2	0	—	1 ¹	1 ¹	34 ¹	14 ¹ (8)	122 ¹²	36 ⁸
IV	13 ⁴	1	5	1	1	0	0	—	7 ²	3 ² (3)	26 ⁶	5 ²
V	30 ⁷	2 ²	14 ³	0	8 ⁶	0	1 ¹	1 ¹	5 ¹	3 ¹ (3)	58 ¹⁸	6 ¹
VI	18 ¹	1	5	1	0	—	0	—	12 ¹	6 ¹ (4)	35 ²	8 ¹
VII	33 ⁴	2	17 ²	1	9 ⁸	4 ⁴	2 ²	1 ¹	5 ¹	1 ¹ (1)	66 ¹⁵	9 ⁶
VIII	35 ⁷	5 ³	12 ³	0	4 ³	0	1 ¹	0	9 ²	7 ² (3)	62 ^{18†}	13 ⁵
IX	7	1	1	0	0	—	0	—	7	4 (3)	15	5
X	5	1	2	0	1	0	1	—	3 ¹	3 ¹ (2)	12 ¹	5 ¹
XI	6	0	1	0	0	—	0	—	11 ¹	6 ¹ (4)	18 ¹	6 ¹
XII	8 ¹	1	3 ¹	0	0	—	0	—	5 ¹	2 ¹ (2)	16 ³	3 ¹
XIII	9	4	5	3	0	—	0	—	9 ¹	8 ¹ (5)	23 ¹	15 ¹
XIV	14 ³	5 ²	7 ¹	0	1 ¹	1 ¹	0	—	7 ²	4 ² (2)	29 ⁷	10 ⁵
XV	8	1	1	0	0	—	0	—	6	4 (2)	15	5
XVI	6 ¹	3	1	0	0	—	0	—	2	0	9 ¹	3
XVII	11	3	1	0	0	—	0	—	8 ¹	5 ¹ (3)	20 ¹	8 ¹
XVIII	15 ²	5	4 ¹	0	1 ¹	0	0	—	15	7 (7)	35 ⁴	12
XIX	18	4	5	1	0	—	0	—	11	5 (4)	34	10
XX	3	1	3	0	0	—	0	—	12 ³	6 ³ (4)	18 ³	7 ³
XXI	2	1	1	0	0	—	0	—	4	2 (2)	7	3
XXII	0	—	3	1	0	—	0	—	1	1	4	2
XXIII	3	0	0	—	0	—	0	—	2	1 (1)	5	1
XXIV	3	1	1	0	0	—	0	—	3	1 (1)	7	2
XXV	8 ³	3 ²	2	1	0	—	0	—	3 ¹	2 ¹ (2)	13 ⁴	6 ³
XXVII	0	—	0	—	0	—	0	—	1	0	1	0
XXVIII	6	1	3	1	0	—	0	—	7 ¹	4 ¹ (3)	16 ¹	6 ¹
XXIX	4	2	4	1	0	—	0	—	9 ¹	4 ¹ (4)	17 ¹	7 ¹
XXXI	0	—	1	1	0	—	0	—	4	0	5	1
XXXII	0	—	0	—	0	—	0	—	1	0	1	0
Not I-XXXII	5 ³	3 ³	2	0	0	—	0	—	2	0	9 ³	3 ³
Total	446 ⁶⁹	79 ²⁴	153 ¹⁸	16 ¹	72 ³⁷	12 ¹¹	16 ¹⁰	5 ⁴	220 ²⁴	109 ²⁴ (79)	911 ^{158†}	222 ⁴⁴
Per cent Died	17.7		10.5		16.7		31.3		49.5		24.4	

Superscripts represent numbers of cases in which pneumococci were cultured from the blood.

* Three patients received serum alone, no deaths; † 1 received serum alone and died.

‡ Includes 4 serum treated cases.

§ Parentheses enclose numbers of cases typed after death.

half of the 88 patients who received the combined treatment had positive blood cultures and 17 of them died, a mortality of 19.3 per cent. The mortality among the patients who received no specific therapy (except sulfanilamide in a few instances) was very high (49.5 per cent). In more than three-fourths of the fatal cases of this group, however, the etiological diagnosis, and usually the anatomical diagnosis as well, was first made at autopsy. Most of these patients, as will be seen later (tables 2 and 3), were being treated primarily for other serious illnesses, of themselves highly fatal.

The occurrence of some of the more important prognostic factors and their effect on the mortality are shown in table 2. The gross mortality in the 518 patients who were treated with sulfapyridine, alone or with serum, was 17.4 per cent, as compared with a death rate of 12.4 per cent among the 169 cases who received sulfathiazole, with or without serum. These two groups of cases were quite comparable with respect to all the factors listed in the table with one important exception, namely, with respect to the

TABLE II (Continued)

Prognostic Factor	Sulfapyridine Alone or with Serum				Sulfathiazole Alone or with Serum				No Specific Therapy				All Cases*			
	Num-ber	Died	Per cent Died	Inci-dence, per cent	Num-ber	Died	Per cent Died	Inci-dence, per cent	Num-ber	Died	Per cent Died	Inci-dence, per cent	Num-ber	Died	Per cent Died	Inci-dence, per cent
Extent of lesion																
Single lobe	332	37	11	64	118	10	8	70	78	15	19	35	531	62	12	58
Multiple lobes	82	14	17	16	17	2	12	10	13	4	31	6	112	20	18	13
Unilateral	104	40	38	20	34	9	26	20	129	90	70	59	268	140	52	29
Bilateral																
Day treatment begun																
First	47	9	19	9	15	0	0	9								
Second	105	12	11	20	28	1	4	17								
Third	79	6	8	15	31	5	16	18								
Fourth	81	11	14	16	37	5	14	22								
Fifth	76	10	13	15	14	1	7	8								
Sixth	35	3	9	7	16	2	13	9								
Seventh or later	58	19	33	11	23	4	17	14								
Not known	37	21	57	7	5	3	60	3								
Admitted: Before Feb. 1	318	48	15.1		0	—	—		138	60	43.5		460	109	23.7	
After Feb. 1	200†	43	21.5		169	21	12.4		82	49	59.8		451	113	25.1	
Totals	518	91	17.4	100	169	21	12.4	100	220	109	49.5	100	911	222	24.4	100

* Including 4 cases treated with serum alone.

† Incidence calculated for cases in which blood cultures were made.

‡ These included 42 bacteremic cases (incidence 21%) with 20 deaths (mortality 48%). There were 33 who received serum in addition to drug with 9 deaths (27%).

age distribution. More than one-half of the deaths among the sulfapyridine treated cases occurred in patients over 60 years of age, whereas only one-third of those treated with sulfathiazole were of this age group. Since patients over 60 years of age were relatively twice as frequent among the former cases and since the mortality within each age group was essentially the same in both groups, this factor alone may account for most, if not all, of the difference in mortality between the sulfapyridine treated cases and those treated with sulfathiazole. This is further suggested by the fact that the mortality in the sulfapyridine treated cases was higher after February 1 than before that time, when all of the cases were treated with that drug.

TABLE III
Serious Antecedent Systemic Complications in Patients with
"Secondary" Pneumococcic Pneumonia

Antecedent Disease	Sulfapyridine Alone or with Serum		Sulfathiazole Alone or with Serum		No Specific Therapy		All Cases	
	No.	Died	No.	Died	No.	Died	No.	Died
Congestive cardiac failure	18	10	7	2	30	23	55	35
Acute coronary occlusion	1	1	2	2	4	2	7	5
Cerebrovascular accident	3	2	2	2	17	16	22	20
Renal failure	4	1	1	1	7	7	12	9
Hepatic disease, severe	4	3	1	0	3	3	8	6
Operations or injuries:								
Head and neck	6	1	0	—	4	2	10	3
Respiratory tract	5	0	2	0	5	2	12	2
Abdomen	23	9	3	1	11	4	37	14
Others	7	2	0	—	0		7	2
Asthma, acute	8	1	4	0	6	2	18	3
Severe infections (non-pneumococcic)	11	5	7	2	15	5	33	12
Poisoning (except alcohol)	4	2	1	1	1	0	6	3
Severe anemia, blood loss	2	1	0	—	4	3	6	4
Malignant tumors:								
Lung	2	2	1	0	4	4	7	5
Others	3	1	2	1	14	13	20	16*
Acute alcoholic intoxication †	36	6	5	3	7	0	48	9
Delirium tremens †	20	4	6	0	3	0	29	4
Pregnancy or puerperium †	10	1	0	—	4	0	14	1

* Include 1 patient treated with serum alone.

† Not included as "secondary" pneumonias.

An appreciable proportion of the specifically treated cases occurred in the course of other serious illnesses, and the mortality in such "secondary" pneumonias was particularly high. This factor also accounted for the high death rate among the patients who received no specific therapy. The primary diseases, in the course of which these secondary pneumonias occurred, are listed in table 3. Of interest also are the cases complicating pregnancy and the puerperium which are listed in this table because of the high expected mortality,² although they are not classified as "secondary" pneumonias. The only death among these cases occurred in a patient whose

pneumonia complicated a septic abortion. The mortality among patients admitted acutely intoxicated from alcohol or who had delirium tremens in the course of their pneumonia was also comparatively low.

Dosage. Sulfapyridine and sulfathiazole were used in identically the same manner. In general, the initial dose was 2 grams followed in two hours by 1 or 2 grams and then 1 gram every four hours. The sodium salt of each was used in occasional cases where vomiting was excessive or where oral dosage was impractical. In such cases an initial dose of 4 or 5 grams, followed by 2 to 3.3 grams every eight to twelve hours were given in sterile physiological saline in concentrations of 0.5 to 5 per cent. It was rarely necessary to give more than three intravenous doses, after which oral therapy was used. The drug was usually discontinued after two to four days of normal temperature, provided the other symptoms of active infection had subsided. Fluids were given liberally, with an attempt being made to attain a daily intake of 3 to 4 liters.

TABLE IV

Dosage of Sulfapyridine and Sulfathiazole Used and the Duration of Acute Illness after Chemotherapy Was Started

	Treated with Sulfapyridine				Treated with Sulfathiazole			
	Alone		With Serum		Alone		With Serum	
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died
Number of Cases *	367 ⁴⁵	79 ²⁴	60 ²⁶	12 ¹¹	137 ¹⁷	16 ¹	11 ⁶	5 ⁴
Average total dose (grams)	23	18	27	33	27	18	41	35
Bacteremic cases	31	14	30	33	27	3	56	39
Non-bacteremic cases	21	20	25	24	27	19	24	23
Number of patients * who received a total dose of:								
5 grams or less	5 ¹	13 ⁶	1	0	0	2 ¹	0	0
6-10 grams	35	23 ⁸	4 ³	1 ¹	4 ¹	3	1	0
11-15 grams	60 ⁴	9 ³	7 ²	2 ²	10 ¹	4	0	1 ¹
16-20 grams	66 ⁴	9 ⁴	10 ²	1 ¹	27 ³	3	0	0
21-25 grams	70 ⁶	7 ¹	8 ³	3 ²	27 ³	2	2	1
26-30 grams	52 ¹¹	4	9 ⁵	0	27 ²	1	2 ¹	1 ¹
31-40 grams	59 ¹²	7	8 ⁴	1 ¹	30 ⁶	0	2 ¹	0
41+ grams	20 ⁷	7 ²	13 ⁷	4 ⁴	12 ¹	1	4 ⁴	2 ²
Number of patients * whose disease terminated after:								
12 hours or less	87 ⁷	10 ⁵	2	0	28 ³	2 ¹	0	0
13-24 hours	93 ¹¹	14 ⁸	11 ⁵	1 ¹	28 ⁵	0	2 ¹	0
25-36 hours	80 ¹²	4 ¹	19 ⁷	1 ¹	31 ⁵	2	3 ¹	1 ¹
37-48 hours	27 ³	5 ¹	5 ³	0	8 ¹	4	1	1 ¹
49-72 hours	26 ⁵	8 ³	6 ³	1 ¹	17 ²	1	0	0
73-96 hours	19 ³	9 ²	5 ²	2 ²	11 ¹	0	2 ¹	0
97-120 hours	12 ¹	4 ²	3 ¹	0	4	2	0	
121 hours or longer	18 ³	25 ²	6 ²	7 ⁶	6	5	2 ²	3 ²
Indeterminate	5	—	3 ³	0	4	0	1 ¹	0

* Superscripts represent numbers of patients with positive blood cultures.

The average total dose actually used in all cases was somewhat greater for sulfathiazole than for sulfapyridine, and doses of more than 25 grams were used in a larger proportion of cases which received the former drug, as noted in table 4. This was true both in patients treated with drug alone and in those who received serum in addition. About one-half of the fatal cases who were given only sulfapyridine, and about one-third of those who were treated with sulfathiazole alone and died, received a total of 10 grams of drug or less.

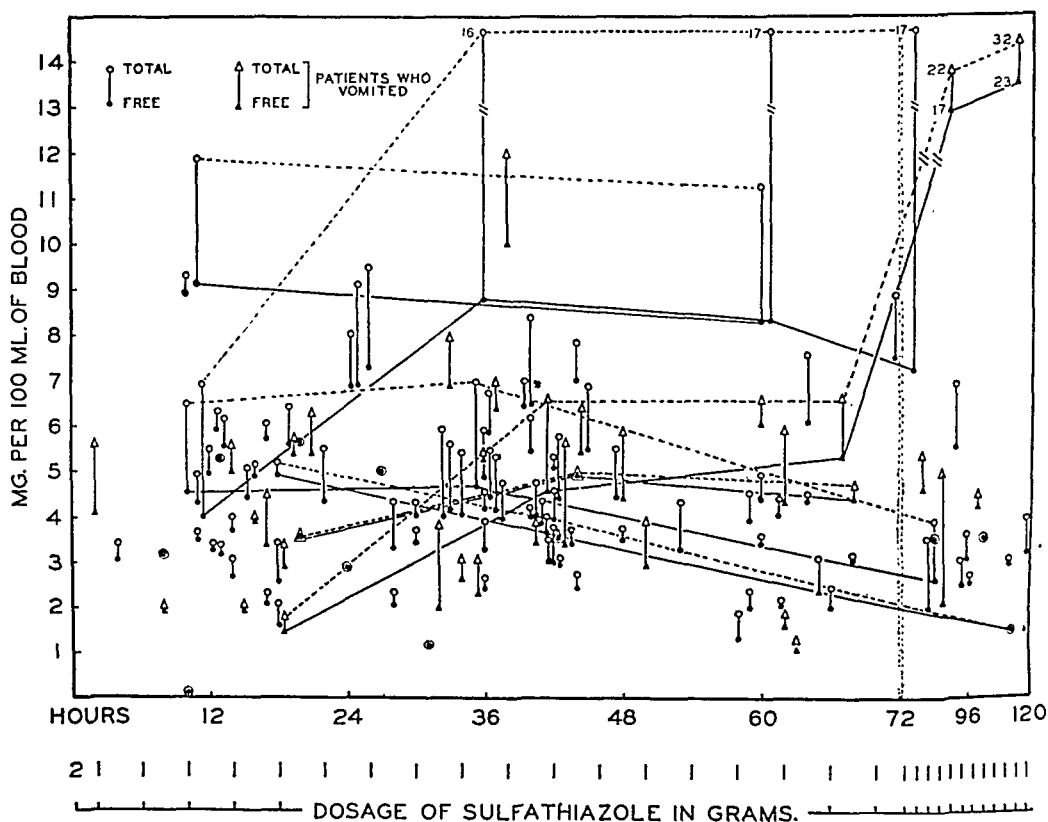


FIG. 1. Blood levels of free and total sulfathiazole in patients who received an initial dose of 2 grams, 1 gram two hours later and then 1 gram every four hours. The lines connect determinations made in the same patient.

The concentrations of sulfathiazole attained in the blood were generally lower than those found after treatment with the same dose of sulfapyridine. In most cases, the concentration of free sulfapyridine ranged between 3 and 9 mg. per cent, while the levels of free sulfathiazole ranged between 2 and 6 mg. per cent. Large amounts of acetylated drug were usually present in the blood of sulfapyridine treated cases, and constituted from 20 to 50 per cent of the total circulating drug. Only small amounts of acetylated drug were found in sulfathiazole treated cases, except in occasional patients with nitrogen retention. In figure 1 are shown the blood levels in a group of consecutive patients, all of whom received identical dosage of sulfathiazole.

This figure may be compared with a similar one previously published,¹ in which the levels on the same dose of sulfapyridine are charted in the same manner. Wide variations were noted, and these were not related to vomiting. The patients showing the highest levels of sulfathiazole all had high blood non-protein nitrogen levels at the same time.

Serum was given in divided doses, beginning with an initial injection of 1 or 2 c.c., after the usual precautions. Concentrated rabbit serums were used in almost every case. Nearly all the patients received either two or three doses, two hours apart, intravenously. Occasional patients were given part or all of the serum intramuscularly. The total amount given was 40 c.c. or less, and usually contained between 50,000 and 400,000 units. Doses greater than 200,000 units were used in 23 patients, of whom nine died. In the majority of cases, the first dose of serum was given from 12 to 36

TABLE V

Relation of Serum Administration to Drug Therapy and to the Termination of the Disease in Patients Receiving Combined Therapy

A. Interval from first dose of drug to first dose of serum					B. Duration of acute illness after first dose of serum				
Hours	Sulfapyridine		Sulfathiazole		Hours	Sulfapyridine		Sulfathiazole	
	Recovered	Died	Recovered	Died		Recovered	Died	Recovered	Died
12 or less	7 ²	2 ²	1 ¹	2 ²	12 or less	38 ¹⁶	3 ³	7 ³	1 ¹
13-24	21 ⁹	4 ⁴	3 ²	2 ¹	13-24	9 ³	—	—	—
25-36	15 ¹⁰	1	4 ¹	—	25-36	5 ²	—	—	—
37-48	3 ¹	1 ¹	2 ¹	—	37-48	3 ²	1 ¹	—	1 ¹
49-72	5 ¹	2 ²	1 ¹	—	49+	5 ^{4*}	8 ⁷	4 ^{3*}	3 ²
73+	9 ⁴	2 ²	—	1 ¹					
Total	60 ²⁷	12 ¹¹	11 ⁶	5 ⁴	Total	60 ²⁷	12 ¹¹	11 ⁶	5 ⁴

Superscripts represent numbers of bacteremic patients.

* Includes cases in whom empyema obscured the termination of the pneumonia.

hours after the first dose of drug, but a considerable number of patients first received serum on the third day of chemotherapy or later (table 5).

Duration of Acute Illness after the Beginning of Treatment (tables 4 and 5). Among the patients who recovered, 71 per cent of those treated with sulfapyridine alone and 63 per cent of those treated with sulfathiazole alone were afebrile and essentially symptom free within 36 hours after the first dose of the chemical. About one-half of those who received serum in addition and recovered were afebrile within the same interval after the drug was started. However, more than one-half of the latter had a crisis within 12 hours after the first dose of serum.

Untoward Reactions. The toxic effects of sulfapyridine and sulfathiazole in the cases of pneumococcic pneumonia are listed in table 6. With the former, the symptoms noted and their frequency were essentially similar to those observed in the previous year. In the sulfathiazole treated

cases nausea and/or vomiting was noted in 42 per cent of the cases, as compared with 54 per cent among sulfapyridine treated cases. Vomiting of moderate or severe degree was, however, uncommon with the former and quite frequent with the latter, in spite of the application of a large variety of measures aimed to prevent or alleviate this symptom. In five of the sulfapyridine treated cases the vomitus contained moderate to large amounts of blood. Four of these patients died; in two of them the source of bleeding was found in the small intestine and in a third it originated in esophageal varices.

TABLE VI
Numbers of Patients Showing Various Untoward Effects from Chemotherapy

Toxic Effect	Sulfapyridine (518 cases)	Sulfathiazole (169 cases)
Nausea and/or vomiting:	279	71
Nausea alone	30	13
Mild vomiting	94	38
Moderate vomiting	120	19
Severe vomiting	35	1
Hematemesis	5	0
Diarrhea	2	0
Hematuria:		
Gross	6	3
Microscopic	8	2
Crystals (acetylated drug?) in urine	18	20
Nitrogen retention in blood *	18	3
Anemia †	13	1
Leukopenia ‡	7	1
Drug rash	5§	5
Drug fever	13	8
Fever after drug stopped	14	6
Relapse of pulmonary infection	22	3
Delirium or depression	11	2
Toxic hepatitis	0	1

* Increase of 20 mg. per cent or more of non-protein nitrogen during treatment.

† Drop of 20 per cent or more in hemoglobin during treatment.

‡ Drop in leukocyte count below 4000 per cu.mm. during treatment. One of sulfapyridine treated cases died of agranulocytosis.

§ Includes one with mucous membrane lesions.

|| During treatment or within 10 days of the time the drug was discontinued.

Hematuria was about as frequent with the one drug as with the other. In most instances it was discovered only on microscopic examination of the urine. Nitrogen retention was more frequent in the sulfapyridine treated cases. Characteristic crystals presumably of the acetylated form of the drug, were seen on microscopic examination of the voided urine and were more frequent in the sulfathiazole treated cases. The crystals were often seen in the specimen bottles after the urine was allowed to stand for a while. Microscopically, the sulfapyridine crystals appeared in irregular clumps of blade-like crystals, while the sulfathiazole crystals were long and thin and the clumps assumed forms like sheaves of wheat.³ Crystals were seen in almost all of the cases with hematuria.

Anemia and severe leukopenia were considerably more frequent in the sulfapyridine recipients. One of the latter died of agranulocytosis which developed on the sixteenth day of treatment. Leukopenia has been noted more frequently among patients treated with sulfathiazole for conditions other than pneumococcic pneumonia. One such patient died of agranulocytosis during the fourth week of treatment for subacute bacterial endocarditis.¹¹

Drug fevers and drug rashes were more frequent with sulfathiazole. Three of the rashes observed were accompanied by typical lesions of erythema nodosum on the extensor surfaces of the arms and legs, particularly around the knees and elbows. Two of the latter had erysipeloid lesions of the face with edema of the eyelids, but the scleral and conjunctival lesions described by Haviland and Long⁴ were not seen. Rashes and fevers were both seen with even greater frequency among cases treated with sulfathiazole for other diseases.

Relapses of fever and symptoms and reactivation of the pulmonary lesion were frequent. They usually occurred within 48 hours after the drug was discontinued—sometimes after an obviously inadequate total dose. In three of the cases these relapses were associated with a different type of pneumococcus; in three instances they were probably related to the acquisition of fastness by the original infecting pneumococcus⁶; in three others bacteremia with the same type recurred during or after two to six days of drug therapy; while in several patients no pneumococci could be found after thorough search of typical, freshly raised rusty sputum obtained at the time of the relapse. The response to further chemotherapy during the relapse varied; some patients had a typical and rapid drop in fever while others failed to respond at all or improved only after specific serum was given. In a number of other patients, fever recurred as soon as the drug was discontinued, although there was no evidence of focal complications or of a reactivation of the pulmonary lesion.

Untoward reactions from specific serums were few and mild. Thermal reactions (chills) occurred in 17 of the 92 serum recipients, including the four who had no chemotherapy. All the chills were mild and only three patients had chills after more than one injection. Immediate reaction in the form of dyspnea and nausea occurred after one of the injections in each of five patients, a typical asthmatic attack occurred in one case and urticaria in another. Serum sickness with arthralgia and/or urticaria was noted in six patients, while seven others had only a low grade fever about one week after the serum administration which may have been a manifestation of serum sickness.

Complications. Postpneumonic complications were of the usual variety and occurred in about the same frequency as in the previous year. Most of the patients in whom infected purulent fluid was obtained by thoracentesis and who recovered eventually required surgical drainage by rib section. In three patients the empyema cleared without such intervention; all of these

TABLE VII
Complications

Complication	Treated with Sulfapyridine				Treated with Sulfathiazole				No Specific Treatment		All Cases
	Alone		Plus Serum		Alone		Plus Serum		Recovered	Died	
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died			
Empyema*	6 ¹	6 ¹	4 ⁴	3 ¹	1	1	3 ³	1	2	4 ³	31
Pericarditis	—	1	—	—	1	—	—	—	—	4 ³	6
Endocarditis, vegetative	—	3 ²	—	2 ²	—	—	—	—	—	7 ⁶	12
Meningitis	—	1	—	1	—	—	—	—	—	1 ¹	3
Peritonitis	—	1	—	—	—	—	—	—	—	1 ¹	2
Arthritis, suppurative	—	1	—	—	—	—	—	—	—	—	1
Lung abscess	—	1	—	—	—	—	—	—	—	—	1
Sterile effusion	11 ²	1 ¹	7 ²	—	9	1	—	—	1	1	31
Atelectasis	5 ¹	—	1	—	1	1	1 ¹	—	2	—	10
Otitis: catarrhal	3	—	—	—	1	—	—	—	—	—	4
suppurative	4	—	—	—	1	—	—	—	—	—	5
Subcutaneous abscesses	1 ¹	—	1	1 ¹	2 ¹	—	—	—	—	—	5
Streptococcus sepsis	—	2	—	—	1	1	—	—	—	—	7
Jaundice	2 ²	1 ¹	3 ¹	1 ¹	1	1	—	—	—	3 ¹	10
Relapse after drug therapy	17 ⁶	—	4 ²	1 ¹	3	—	—	1	—	1	25
Extended during drug therapy	2	—	—	—	3 ¹	—	—	—	—	—	5

Superscripts represent number with positive blood cultures.

* Only 3 recovered without operative drainage (1 treated with sulfapyridine and 2 treated with sulfapyridine and serum). The empyema was of the "putrid" type with mixed bacteriology and probably associated with pulmonary abscess in 6 of the sulfapyridine treated patients (of whom 3 died), and in 1 of the untreated patients who recovered. The one who recovered after sulfapyridine treatment required no surgical intervention.

patients received sulfapyridine and two were given serum in addition. Only small amounts of fluid were obtained in these cases. Of interest is the fact that in seven of the empyemas, six of which occurred in sulfapyridine treated cases and one in a patient who received no specific treatment, the fluid was putrid or subsequently became putrid. These cases were probably associated with abscess formation in the lungs, but this was verified in only one patient who developed a broncho-pleural fistula. Four of these seven patients recovered, including the patient who received no specific treatment and the sulfapyridine treated patient who recovered without surgery.

SULFATHIAZOLE IN NON-PNEUMOCOCCIC PNEUMONIAS

In the period covered in this report, 95 additional patients with pneumonia were treated with sulfathiazole, but bacteriological studies of blood and sputum failed to reveal the presence of pneumococci. In some of these cases the predominant or only organisms cultured were hemolytic streptococci and *Staphylococcus aureus*, but in the majority the sputum yielded only ordinary mouth organisms, predominantly streptococci, which exhibited varying degrees of hemolysis. Among these patients the response to treatment varied much more than among the pneumococcic pneumonias, some showing rapid and dramatic critical recoveries while in others the disease was apparently refractory to the drug. Clinically, 24 were diagnosed lobar pneumonia and 71 atypical or bronchopneumonia. A large proportion of the latter were secondary pneumonias, but some were probably primary pneumococcic pneumonias in which the materials available for bacteriological study were inadequate or unsatisfactory. There were four deaths among the lobar pneumonias and 18 among the atypical pneumonias, giving a mortality of 23 per cent for the entire group. No accurate data are available for a satisfactory evaluation of the results in such cases, but many of them were undoubtedly helped by the drug and some lives were probably saved in this group. To be sure, in some of the cases included under the pneumococcic pneumonias, the relation of the pneumococcus to the disease is not always clear. This is particularly true among the cases with higher types, where the mortality was greater than among those with the more common types.

DISCUSSION

The focus of attention in the treatment of pneumonia at the time of this writing is centered on the relative merit of sulfathiazole and sulfapyridine. From the point of view of the gross mortality, the data at first glance suggest a definite superiority of sulfathiazole. When corrected for the age distribution, however, the mortality with each drug was about the same. Others have found a slightly lower mortality with sulfathiazole in seemingly comparable cases,⁶ but the data from most of the clinics in which this drug received extensive clinical trials are yet to appear and may shed more light

on this point. Laboratory data concerning the relative effectiveness of these drugs are somewhat conflicting.⁷ Our own studies in vitro with freshly isolated strains⁵ indicate that these two drugs have an almost identical effect in equal concentrations on most pneumococcus strains. When differences were noted, they were all slight but they indicated that for some strains sulfathiazole may produce the same effect as sulfapyridine with slightly smaller concentrations.

That the amount and severity of the nausea and vomiting are appreciably less with sulfathiazole is generally agreed, and this alone may be a determining factor in the success or failure of chemotherapy in certain cases. Inadequate dosage is used in some patients, while in others treatment is interrupted or discontinued too soon because of the vomiting. This alone may occasionally result in a fatality that might have been avoided. The frequency of relapses with sulfapyridine, on the one hand, and the greater average total dose of sulfathiazole, on the other, are, in a certain measure, reflections of this effect. Anemia and leukopenias were also less frequent in the sulfathiazole treated cases.

Certain other important untoward effects, notably drug rashes and hematuria, are more frequent and probably more severe with sulfathiazole than with sulfapyridine, as indicated in the present cases and in our general experience with these drugs to date. The renal complications are of particular interest, since the smaller degree of acetylation of sulfathiazole in both blood and urine is usually offered as one of the chief advantages of this drug over sulfapyridine. To be sure, the acetylated form of each of these drugs is inactive therapeutically and is quite insoluble and therefore undesirable. However, the decreased acetylation of sulfathiazole is associated with a much more rapid excretion of the drug into the urine, so that it is more difficult to maintain high levels in the blood while greater concentrations of the drug are excreted into the urine. The opportunities for the development of hematuria and other manifestations of severe renal damage may thus be as great as with sulfapyridine, if not actually greater.^{3, 8}

On the whole, it may be concluded that (1) both sulfapyridine and sulfathiazole are about equally effective in the treatment of the pneumococcic pneumonias and (2) the administration of both of these drugs is accompanied by toxic symptoms which vary somewhat in frequency and severity. Since vomiting is less frequent and less severe with sulfathiazole, this drug is easier to give in adequate doses and is therefore to be preferred in most cases.

The relative merits of serotherapy and chemotherapy and the advantages of using serum early, in addition to drugs, in the severe cases of pneumococcic pneumonia have been discussed in the last year's reports.^{1, 9} The experience of the present season has in no wise altered the conclusions reached at that time.

The gross mortality in all the cases that were treated specifically with chemicals and/or serums during the present year was about the same as in

the previous year. This fact is of interest since a number of American authors who reported unusually low mortality rates during their first year's experience with sulfapyridine were inclined to attribute their favorable results in part to the mild character of the pneumonia during that season. Higher mortalities during the present season, such as were reported by the Philadelphia workers,^{6a, 10} would tend to bear out such an assumption. Our experience, however, has led us to feel that the differences in severity of pneumonia from year to year, at least when one is dealing with the same type of clinical material, are explicable on the basis of the relative frequency of the important prognostic factors such as those analyzed in this and in similar reports.

SUMMARY AND CONCLUSIONS

The essential data concerning the 911 cases of pneumococcic pneumonia treated at the Boston City Hospital between July, 1939 and June, 1940 have been presented and analyzed.

Specific therapy, consisting essentially of sulfapyridine or sulfathiazole, supplemented in some of the cases by type-specific antipneumococcic serums, was used in 76 per cent of the cases, and the gross mortality in these cases was 16.4 per cent.

Sulfapyridine and sulfathiazole were used in the same manner. The results of treatment with these two drugs were essentially the same when due allowance was made for the difference in incidence of patients over 60 years of age.

The administration of both sulfapyridine and sulfathiazole is accompanied by untoward effects which vary somewhat in frequency and severity. Anemia, leukopenia and relapses were more frequent among the sulfapyridine treated cases. Drug rashes were more frequent among the sulfathiazole recipients, while hematuria was about as frequent with the one drug as with the other. The most common toxic effect of both drugs, however, was the nausea and vomiting, and this symptom was considerably less frequent and less severe among the cases treated with sulfathiazole, making this drug considerably easier to give to the large majority of patients.

The authors wish to acknowledge their indebtedness to the various members of the clinical and laboratory staffs of the hospital for their coöperation in making this study possible. The specific antipneumococcic serums and sulfathiazole were furnished by the Lederle Laboratories, Inc. and, in part, by the Squibb Institute for Medical Research.

REFERENCES

1. FINLAND, M., SPRING, W. C., JR., and LOWELL, F. C.: Specific treatment of the pneumococcic pneumonias: an analysis of the results of serum therapy and chemotherapy at the Boston City Hospital from July 1938 through June 1939, *ANN. INT. MED.*, 1940, xiii, 1567-1593.
2. FINLAND, M., and DUBLIN, T. D.: Pneumococcic pneumonias complicating pregnancy and the puerperium, *Jr. Am. Med. Assoc.*, 1939, cxii, 1027-1032.
3. SADUSK, J. F., JR., BLAKE, F. G., and SEYMOUR, A.: Observations on the absorption, excretion, diffusion, and acetylation of sulfathiazole in man, *Yale Jr. Biol. and Med.*, 1940, xii, 681-696.

4. HAVILAND, J. W., and LONG, P. H.: Skin, conjunctival and scleral reactions in the course of therapy with sulfathiazole, *Bull. Johns Hopkins Hosp.*, 1940, lxvi, 313-318.
5. LOWELL, F. C., STRAUSS, E., and FINLAND, M.: Observations on the susceptibility of pneumococci to sulfapyridine, sulfathiazole and sulfamethylthiazole, *ANN. INT. MED.*, 1940, xiv, 1001-1023.
6. (a) FLIPPIN, H. F., SCHWARTZ, L., and ROSE, S. B.: The comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia, *ANN. INT. MED.*, 1940, xiii, 2038-2049.
(b) BLAKE, F. G.: The treatment of pneumococcal pneumonia, *New England Jr. Med.*, 1940, ccxxiii, 661-667.
7. (a) LAWRENCE, C. A.: Bacteriostatic actions of three thiazole derivatives of sulfanilamide upon bacteria in broth cultures, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 92-97.
(b) LONG, P. H., and BLISS, E. A.: Bacteriostatic effects of sulfathiazole upon various microorganisms. Its therapeutic effects in experimental pneumococcal infections, *Ibid.*, 324-327.
(c) MCKEE, C. M., RAKE, G., GREEP, R. O., and VAN DYKE, H. B.: Therapeutic effect of sulfathiazole and sulfapyridine, *Ibid.*, 417-421.
(d) LITCHFIELD, J. T., WHITE, H. J., and MARSHALL, E. K., JR.: The comparative activity of sulfanilamide, sulfapyridine, sulfathiazole and diaminosulfone in Type I pneumococcus infections in mice, *Jr. Pharm. and Exper. Therap.*, 1940, lxix, 166-170.
8. (a) RHEINHOLD, J. G., FLIPPIN, H. F., and SCHWARTZ, L.: Observations on the pharmacology and toxicology of sulfathiazole in man, *Am. Jr. Med. Sci.*, 1940, cxcix, 393-401.
(b) PEPPER, D. S., and HORACK, H. M.: Crystalline concretions in the renal tubules following sulfathiazole therapy, *Ibid.*, 674-679.
(c) LONG, P. H., HAVILAND, J. W., and EDWARDS, L. B.: Acute toxicity, absorption and excretion of sulfathiazole and certain of its derivatives, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 328-332.
(d) KNOLL, A. F., and COOPER, F. B.: Clinical urolithiasis medicamentosa due to sulfathiazole, *Urol. and Cutan. Rev.*, 1940, xlv, 292-294.
(e) STRAUSS, E., LOWELL, F. C., TAYLOR, F. H. L., and FINLAND, M.: Observations on the absorption, excretion and distribution of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole, *ANN. INT. MED.* (In press.)
9. FINLAND, M., LOWELL, F. C., and SPRING, W. C., JR.: Clinical and laboratory studies on the use of serum and sulfapyridine in the treatment of the pneumococcal pneumonias, *New England Jr. Med.*, 1940, ccxxii, 739-747.
10. PEPPER, D. S., FLIPPIN, H. F., SCHWARTZ, L., and LOCKWOOD, J. S.: The results of sulfapyridine therapy in 400 cases of typed pneumococcic pneumonia, *Am. Jr. Med. Sci.*, 1939, cxcviii, 22-35.
11. KENNEDY, P. C., and FINLAND, M.: Fatal agranulocytosis from sulfathiazole, *Jr. Am. Med. Assoc.*, 1941, cxvi. (In press.)

LIVER FUNCTION IN HYPERTHYROIDISM, WITH SPECIAL REFERENCE TO THE GALAC- TOSE TOLERANCE TEST *

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REVIEW OF LITERATURE

THE endocrines may influence the functions of the liver, mainly the glycogenic function.^{1, 2, 3} Claude Bernard regarded glycogen as an internal secretion product of the liver and recognized connections between this substance and other endocrine products.

Experimental data, pathological observations, clinical jaundice in patients with exophthalmic goiter, and liver function studies establish the fact that the liver is frequently damaged in hyperthyroidism.

The evidence in the literature upon which the connection between hyperthyroidism and liver damage has been established will be presented as follows:

(1) experimental; (2) anatomic changes in the liver; (3) clinical cases of jaundice; (4) liver function tests in patients with exophthalmic goiter.

1. *Experimental*: A large proportion of the investigations in this field deals with carbohydrate metabolism. The glycogen content and pathological changes in the liver after feeding small and toxic doses of thyroid, and the influence of the liver on the thyroxine molecule and of thyroxine on the composition of bile have been studied.

Experimental hyperthyroidism has been produced in animals (cats, guinea pigs, dormice) by excessive feeding of thyroid substance (Farrant, 1913).⁴ The studies of Cramer and Krause (1913)⁵ demonstrated that the addition of thyroid to the diet of cats and rats resulted in almost total disappearance of glycogen from the liver. Parhon (1913)⁶ and Kuriyama (1917-1918)⁷ confirmed this observation also in rabbits. The former attributed the glycogen depletion in the liver to an inhibition of glycogenic function, the latter to an increased glycogenolysis in the liver. Similar confirmatory studies have been reported by Abelin and Jaffe (1920),⁸ Romeis (1923),⁹ Fukui (1925),¹⁰ Boesl (1928),¹¹ Abderhalden and Wertheimer (1928),¹² Abelin and Spichtin (1930),¹³ Lawrence and McCance (1931),¹⁴ Knittel (1931),¹⁵ Althausen and Thoenes (1932),¹⁶ Coggeshall and Greene (1933),¹⁷ and Frazier and Frieman (1935).¹⁸ Fukui (1925) found liver glycogen depletion in rats so uniform that he suggested it as

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a method of assay for thyroid preparations. Frazier and Frieman (1935), however, could not confirm the direct relationship between thyroid dosage and glycogen depletion. Himmelberger (1932)¹⁹ reported the disappearance of liver glycogen in mice after the injection of blood or urine from hyperthyroid subjects. Eitel, Loehr and Loeser (1933-34)²⁰ injected guinea pigs with the thyrotropic substance from the anterior lobe of the pituitary and found a decrease in liver glycogen. Removal of the thyroid gland prevented this effect. Kuriyama (1918), Frazier and Frieman (1935), and Loeser (1934) found that the glycogen depletion could not be prevented by the feeding of large amounts of carbohydrate. Wilder and Sansum (1926)²¹ concluded from studies of the respiratory quotient that the carbohydrate is adequately utilized, the decreased glycogen being probably due to faulty storage of carbohydrate in hyperthyroidism.

The influence of thyroxine on tissue oxidation has been measured. Reinwein and Singer (1928)²² demonstrated an increased use of oxygen by living liver cells when this substance was applied to them in certain concentrations; an inhibiting effect was noted in higher concentrations. According to Dresel, Goldner, and Himmelweit (1929)²³ thyroxine has only a slight direct effect if any at all on tissue oxidation. After the injection of thyroxine, split products derived from proteins appear in the liver in increased amounts. It is these, and especially tyrosin, which they held responsible for the elevated rate of oxidation. The thyroxine leads to increased output of tyrosin, and tyrosin, in turn, combining with iodine in the thyroid, builds thyroxine. In 1925, Schryver²⁴ found that the livers of thyroid-fed animals showed a greater degree of autolysis after 24 hours than those of non-thyroid-fed control animals. However, when thyroid was fed for eight days or more an opposite effect was noted.

The prolonged feeding of thyroid produces other changes in the liver which more than offset the loss of weight due to lack of glycogen or the possible increase of cellular activity. Higgins (1933)²⁵ found that the livers of rats fed a thyroid ration increased in size and also in the extent of the restoration of the liver following partial surgical removal. Simonds and Brandeis (1930)²⁶ had noted a similar relative increase in the weight of the liver in thyrotoxic dogs. Hoskins (1916)²⁷ and Hewitt (1919-1920)²⁸ earlier observed relatively heavier livers in thyroid-fed rats.

The rôle of the liver in thyroxine metabolism has been investigated. Zavadovsky and Perelmutter (1927)²⁹ found that the liver of fowls played an important rôle in decomposition and excretion of thyroxine. Blum and Grutzner (1920)³⁰ demonstrated in dogs the power of the liver to decompose thyroxine and split up iodine-containing fractions into more elementary forms. Kendall (1919)³¹ administered 200 mg. of thyroxine to dogs and in less than 20 hours 43 per cent of the iodine elements of the thyroxine had been excreted in the bile. Kraye (1928),³² working with rats, obtained results similar to those of Kendall.

Thyroxine administration may alter the composition of liver bile. Leites

and Isabolinskaja (1933)³³ found an increase in cholesterol concentration in the bile and in most cases an absolute increase of the amount of cholesterol excreted in a 24 hour collection. The total bile acids and the amount of biliary secretion were also increased. The calcium and potassium content remained unchanged. Besuglow and Tutkewitsch (1933),³⁴ using the same experimental method, reported a fall in cholesterol concentration of bile after the injection of 2 mg. of thyroxine and a rise after total thyroidectomy. Parhon and Werner (1931)³⁵ reported findings similar to those of the latter workers. Johnson and Riegel (1939)³⁶ were unable to demonstrate any effect on the cholesterol concentration or total cholesterol output of the hepatic bile in thyroid-fed or thyroxine-injected dogs despite the fact that the blood cholesterol fell considerably. Following total thyroidectomy the bile cholesterol remained unchanged, although the blood cholesterol rose considerably.

Experimental hyperthyroidism may result in hepatic changes. Farrant (1913) noticed fatty degeneration at the center of the lobules in rabbits. Hashimoto (1921)³⁷ found parenchymatous degeneration of the liver cells about the efferent veins varying from fatty degeneration to necrosis. These changes were sometimes found throughout the lobule, but were never confined to the periphery. Hypertrophy of liver cells, mitotic figures and double nuclei were found in the peripheral zones. While the evidence of chronic passive congestion coincided with marked myocardial changes, the parenchymatous degeneration did not. Gerlei (1933)³⁸ obtained centrilobular necrosis in rabbits after five to seven days with fatal doses of thyroxine subcutaneously.

The possibility that excessive thyroid feeding may potentiate the action of toxic agents was not supported by observations of Davis and Whipple (1919)³⁹ which indicated that thyroid feeding of dogs did not aggravate the liver injury following chloroform anesthesia. Cameron and Karunaratne (1935)⁴⁰ tested the above hypothesis by feeding albino rats large doses of thyroid extract and then determining their minimal toxic dose for carbon tetrachloride. No alteration was found from the dose previously estimated for normal control animals from the same litters.

2. *Anatomical Changes in Hyperthyroidism:* The anatomical changes in the liver in exophthalmic goiter have been reviewed by Weller (1932-1933),⁴¹ Haban (1933-1934),⁴² Beaver and Pemberton (1933),⁴³ Rössle (1933),⁴⁴ and Cameron and Karunaratne (1935). Distinction has been drawn between two main groups of anatomical changes in the liver depending on whether or not passive venous congestion is deemed responsible for pathological changes. The changes noted in the non-congestive cases have been interpreted as representing reactions to varying degrees of injury, the result of thyroid derangement. The pathological changes resolve themselves into three main types: (1) Acute degenerative hepatic lesions in the form of marked fatty change and actual necrosis of either focal or central type, the latter appearing to represent an accentuation of the same toxic

reactions which usually resulted in the fatty change. The fatty degeneration appears to progress sometimes to necrosis and sometimes to chronic changes such as: (2) Atrophy, local or general, or (3) Cirrhosis. Combinations of all forms exist. In rare instances acute liver atrophy has been reported. To these Rössle (1933) added the changes of "serous hepatitis" with capillary alterations. This type of change was not found in cases examined by Zeldenrust and Van Beek.⁴⁵ Thus the pathological changes may be grouped under seven headings: passive congestion, fatty changes, atrophy, cirrhosis, cellular infiltration, necrosis and regeneration.

The complete absence of glycogen in livers of patients who died of exophthalmic goiter has been reported by Pettavel (1914)⁴⁶ and Wegelin (1926).⁴⁷

The co-existence of cirrhosis of the liver and thyroid disease was first referred to by Paul (1865),⁴⁸ and by Trousseau (1868).⁴⁹ Subsequently, Farner (1896),⁵⁰ Askanazy (1898),⁵¹ Dinkler (1900),⁵² Marine and Lenhart (1911),⁵³ Landau (1911),⁵⁴ Pettavel (1912),⁵⁵ Rautmann (1915),⁵⁶ and Holst (1923)⁵⁷ referred to cases of cirrhosis as a complication of exophthalmic goiter. Descriptions of the cirrhotic changes have been given by Marine and Lenhart (1911), Haban (1933-1934), Weller (1933), Rössle (1933), Beaver and Pemberton (1933), and Cameron and Karunaratne (1935). Although similar changes may occur in various chronic diseases in the same age groups, Weller and Haban intimate that the increased incidence and degree of portal changes and fibrosis in the subjects with thyroid disease suggest the existence of a distinctive type of thyroid cirrhosis, e.g., cirrhosis basedowiana (Haban). The chronic changes in the liver result in general atrophy with a decrease in size and weight of this organ. In these cirrhotic livers a characteristic is the presence in certain areas of dilatation of the portal canals with surrounding lymphocytic infiltration, without general alteration in lobular structure. More advanced stages of this lesion occur in which the widened portal canals become united by narrow bands of connective tissue. There may be considerable alteration in the lobular structure, and also annular fibrosis encircling hepatic lobules. "Nodule" formation may be found mainly along the surface or along the edge of the liver, and occasional nodules occur in the deeper portions of the organ. These nodules are well outlined by fibrous tissue bands and bordered by grooves or depressions. Microscopically there is evidence of regeneration in both the liver cells and ducts.*

Significant decrease in the size and the weight of the liver has been reported by Beaver and Pemberton and by Cameron and Karunaratne. Bar-

* The incidence of chronic changes in the livers of patients who have died of Graves' disease varies in published reports. Weller⁴¹ found what he called patchy chronic parenchymatous interlobular hepatitis in 65 per cent of his cases of exophthalmic goiter and in only 2 per cent of a controlled series. The liver changes were irregularly distributed; many lobules appeared normal. Beaver and Pemberton⁴³ observed what they termed subacute toxic atrophy and toxic cirrhosis in 60 per cent of the cases. Cameron and Karunaratne⁴⁰ found cirrhosis in the insular, interinsular or annular stages in 10 of their series of 30 cases (33 per cent).

tels (1938) ⁵⁸ compiled and compared the published weights of normal livers and of the hyperthyroid series of Rössle, Cameron and Karunaratne and Beaver and Pemberton and found that the weight of 50 normal livers (Boyd 1933) ⁵⁹ averaged 1424 grams compared with the average weight of 1232 grams for 167 hyperthyroid livers. This is contrary to the experimental observations of Simonds and Brandeis (1930) on dogs rendered thyrotoxic by feeding desiccated thyroid. In these animals, even though the loss of body weight was severe the liver lost relatively little weight. Apparently the results of the experimental observations cannot be transferred to cases of exophthalmic goiter. There does, however, appear to be a direct relationship between the loss of body and liver weights, the extent of the pathological process, and the clinical severity of the disease in a correlation of clinical and postmortem data (Beaver and Pemberton). There also appears to be a correlation between the pathological findings in the liver and the duration of the clinical history, on the whole. Cameron and Karunaratne found that the cases of more advanced cirrhotic changes gave a longer history (one to three years at least) and those with less advanced lesions, i.e., insular or interinsular fibrosis (four months to two years).

3. *Clinical Jaundice*: The jaundice which occurs in the course of exophthalmic goiter has, in rare instances appeared to be explainable by the associated congestive heart failure. In the majority of cases, however, the thyrotoxic disease itself appears to be the direct cause of the jaundice. In occasional instances the jaundice is due to associated intercurrent disease of the liver and bile passages.

The occurrence of jaundice has been mentioned in the communications of Habershon (1875),⁶⁰ Eger (1880),⁶¹ Gaill (1883),⁶² Strümpell (1886),⁶³ Burton (1888),⁶⁴ Westedt (1889),⁶⁵ Boinet and Bourdillon (1891),⁶⁶ Moebius (1896),⁶⁷ Sutcliff (1898),⁶⁸ Dieulafoy (1901),⁶⁹ Sattler (1906),⁷⁰ Rautmann (1914-1915),⁶⁶ Chvostek (1917),⁷¹ Marine and Lenhart, Crotti (1922),⁷² Boothby (1922),⁷³ Klose (1929),⁷⁴ Barker (1930),⁷⁵ Assmann (1931),⁷⁶ Heilmeyer (1931),⁷⁷ Lichtman (1932),⁷⁸ Beaver and Pemberton (1933), Retzlaff (1937).⁷⁹

In every instance of jaundice complicating hyperthyroidism an unrelated cause for jaundice must be ruled out. Assmann (1931) emphasized this fact and Lichtman (1932) referred to two cases of terminal jaundice complicating thyrocardiac disease in which the jaundice was accounted for by cholangitis histologically. Clinically it had appeared that the jaundice was directly connected with the thyrocardiac disease. Assmann emphasized the possible association of hyperthyroidism with cholelithiasis, syphilis, and other common causes for jaundice. Eder (1906) ⁸⁰ maintained that the jaundice arose from some chronic intestinal toxemia, and that possibly the same intoxication precipitated the hyperthyroidism. Boothby (1922) noted that clinical jaundice was not uncommon in the late stage of long continued gastrointestinal crises in cases of Graves' disease. Crotti (1922) also re-

ferred to the yellow tint of the sclerotics which may occasionally be observed in thyrotoxic patients during severe gastrointestinal disturbances.

Outspoken jaundice of the skin and sclerae is rare in exophthalmic goiter. The observation of Beaver and Pemberton would indicate that jaundice occurred in approximately 20 per cent of 107 cases. However, in approximately 75 per cent of their cases the jaundice was extremely mild (Grade 1), and in only one instance was it severe. The general impression exists that jaundice occurs only in the severe thyrotoxic cases. Approximately one-third of cases with jaundice in Beaver and Pemberton's series were in or on the verge of thyroid crises before death.

In the course of a decade, Dr. Paul Klemperer, Pathologist to the Mount Sinai Hospital, has made anatomical examinations in 26 cases of Graves' disease. Jaundice occurred in only two instances (8 per cent). The ages of these patients were 30 and 34 years respectively and they had suffered from Graves' disease over a period of seven and two years respectively. There was no heart failure in either case and the jaundice was attributed directly to Graves' disease.

4. *Liver Function in Hyperthyroidism:* The appearance of jaundice in the course of thyrotoxicosis and a search for the cause of the thyroid crisis have led to repeated studies of the functional activity of the liver in clinical hyperthyroidism. Bauer, when he introduced the galactose tolerance test, noted a disturbance in the tolerance for this sugar in Graves' disease. Hirose (1912)⁸¹ found that patients with hyperthyroidism had an alimentary galactosuria similar to that found in cirrhosis and catarrhal jaundice. This was confirmed by Strauss (1913, 1930).⁸² Sanger and Hun (1922)⁸³ found abnormal glucose tolerance curves in hyperthyroidism which they attributed to a failure of the liver to store glucose, due to some toxic change in the liver. Youmans and Warfield (1926) found a moderate degree of disturbance in dextrose and levulose tolerance. They concluded that there appeared to be no proportionality between the degree of impairment of liver function and the increase of the metabolic rate. There was some correlation between the loss of weight and the disturbance of liver function in 10 cases of exophthalmic goiter. Kugelman (1930)⁸⁴ obtained evidence of a disturbance of hepatic function by means of the levulose tolerance test. Adler and Lemmel (1928)⁸⁵ noted abnormal ester cholesterol partition in a few cases of severe exophthalmic goiter. The ester fraction was decreased as in cases of liver damage. They attributed fatty stools sometimes observed in this disease to disturbed fat metabolism.

The change in carbohydrate metabolism in exophthalmic goiter, as evidenced by a depletion of glycogen in the liver, was made the basis of a biological test for thyroxine by Dresel and Goldner (1929)⁸⁶; and Willis and Mora (1931)⁸⁷ applied this principle as a biological test for hyperthyroidism using the liver of the mouse as a test object. Himmelberger (1932) adapted the technic of the mouse test for urine as well as blood serum of patients with Graves' disease.

Some evidence of bile pigment metabolism disturbances in hyperthyroidism has been reported. Youmans and Warfield (1926) studied the liver function in 44 cases of thyrotoxicosis, including cases with passive congestion of the liver by means of the phenoltetrachlorophthalein test. They found retention of 3 to 10 per cent of this dye in the blood after 60 minutes in 22 of 48 cases (45 per cent) and elevated icterus index in seven of nine cases. Seven patients in the series were clinically jaundiced. Passive congestion and pneumonia may have contributed to the pigment metabolism disturbance independently of thyroid disease. These authors could detect no hepatic functional impairment, as measured by the dye excretion test in dogs that had been fed a large amount of thyroid extract. Heilmeyer (1931) found the urobilin quotient (urine/stool urobilin) to be elevated in three of six cases investigated. As tested by the method of Bergmann and Eilbott (1927)⁸⁸ the bilirubin excretion power of the liver was found to be impaired in five cases. Toxic injury of the liver due to thyroid hormone rather than circulatory failure was considered to be responsible.

Maddock, Collier and Pedersen (1936)⁸⁹ studied the liver function by means of the bromsulphalein dye test and serum bilirubin. Of 13 patients with toxic goiter 8 or 61 per cent showed evidence of liver damage before operation as measured by an increase in serum bilirubin above 3 mg. per liter and above 10 per cent bromsulphalein dye retention. There appeared to be some correlation between the severity of the hyperthyroidism, as measured by basal metabolic rate, and the functional impairment. In five hyperthyroid patients with normal function tests the basal rate averaged 33 per cent as compared with an average of 54 per cent for eight patients with abnormal liver function tests. A relation was found to exist between the severity of the disease and the degree of liver damage. There was no correlation between the level of preoperative liver function impairment and the incidence of postoperative reactions. In the postoperative period an increase in the incidence and degree of impaired hepatic function and an increase in hyperthyroid reactions were found but there was no evidence to show that one was the cause of the other. Furthermore, direct relationship between impaired liver function and thyroid crisis has been disclaimed by Foss, Hunt and McMillan (1939).⁹⁰ Lichtman⁷⁸ found no significant increase in the icterus index in thyrotoxic cases without heart failure.

Bartels⁵⁸ observed reduced liver function by means of the hippuric acid excretion test in a high proportion of cases of hyperthyroidism (87 per cent). No apparent correlation was found to exist between the liver function and the duration of hyperthyroidism. The degree of change in liver function was found to be directly related to the severity of hyperthyroidism as measured by the basal metabolic rate and the degree of weight loss. Three months after thyroidectomy normal liver function was restored in a high per cent of cases indicating that the liver damage is rarely permanent. A high carbohydrate diet apparently improved the liver function as measured by this test.

Ragins (1936)⁹¹ applied the Takata-Ara reaction to cases of exophthalmic goiter and found positive reactions in six cases. A negative reaction was obtained in seven cases of exophthalmic goiter and one in toxic adenoma. Madden, Winslow, Howland and Whipple (1937),⁹² studying blood plasma protein in regeneration found that powdered thyroid fed in doses sufficient to accelerate body metabolism showed no distinct effect on plasma protein production which was not attributable to the protein in the thyroid powder itself.

Althausen and Thoenes (1932)⁹³ applied a modification of the dextrose tolerance test followed by an injection of epinephrine. Typical hypoglycemia was not produced. In patients with liver disease characterized by lowered glycogen content of the liver, this modified dextrose tolerance test is followed by hypoglycemia. The impaired function of the liver would appear then to be dependent on factors other than depletion of liver glycogen. Althausen and Wever (1937)⁹⁴ endeavored to obtain further information as to the cause of decreased sugar tolerance in hyperthyroidism by studying the response of patients with this disease to galactose.* The curve of galactose in the blood after oral administration with sugar was higher in patients with hyperthyroidism than in normal or diabetic subjects. The changes in galactose tolerance were not proportionate to the severity of hyperthyroidism judging by any one criterion. This was deemed not remarkable considering that the basal metabolic rate and other manifestations of hyperthyroidism do not necessarily correspond in severity. Thyroidectomy in most instances restored normal tolerance to galactose. The estimation of amino-acid nitrogen in the blood proved to be normal.

Lichtman (1932)⁷⁸ found a disturbance of cinchophen oxidation in 16 of 20 (80 per cent) cases of uncomplicated hyperthyroidism. The capacity of the liver cells to oxidize this substance was moderately impaired. Larger than normal amounts of oxy-cinchophen, a partial oxidation product of cinchophen, appeared in the urine after a test dose. With this test there was in no instance evidence of severe impairment and no direct relationship was noted between the degree of liver damage and level of metabolic rate, duration of the disease, or degree of weight loss.

PERSONAL OBSERVATIONS

In the course of the development of a modification of the technic for the performance of the galactose tolerance test based on a differentiation of galactose and glucose in urine by means of yeast fermentation after the oral

* The value of the galactose test as a study of liver function in patients with hyperthyroidism is not, in our opinion, depreciated by Althausen's observation⁹⁵ that there is an increased rate of absorption of galactose from the intestinal tract in this disease. This may be due to the associated increased rate of blood flow through the tissues in this disease. There is also, however, a coincident increased rate of oxidation of carbohydrate in the tissues. On the basis of an increased rate of absorption alone, it is, therefore, erroneous to conclude that the status of galactose tolerance as a liver function test is necessarily altered in hyperthyroidism. Furthermore, the fact that 54 per cent of the galactose tolerance tests in our series of cases of hyperthyroidism gave normal results suggests that increased intestinal absorption of galactose is not the underlying factor in the pathological galactosurias.

ingestion of the standard dose of galactose,⁹⁶ observations were made on the galactose tolerance in 13 patients with thyrotoxicosis.* The results indicated a normal galactose excretion varying between 1.1 and 2.4 grams in seven of 13 cases (54 per cent) (table 1). In the remaining six cases

TABLE I
Thyrotoxicosis and Normal Galactose Tolerance

Case No.	Age	Sex	Weight Loss Lbs.	Duration of Disease Months	B.M.R. Per Cent	Galactosuria,* Grams
1. S. S.	14	F	15	2	+24-12†	1.2 (Lugolization before Admission-Remission Stage)
2. L. S.	19	F	0	2nd stage	+26-9	1.4 (1st stage Thyroidectomy 6 months previously)
3. S. A.	33	F	30	6	+33-23	1.6
4. C. B.	40	F	10	5	+84-25	1.4
5. A. K.	41	F	24	3.5	+29-26	2.2
6. M. K.	50	M	5	3	+35-22	1.1
7. I. D.	55	F	50	12	+52-52	2.4 2.4 (Congestive Heart Failure)
Average	33		19	5.3	+40-25	

* Galactose tolerance performed before or promptly after the beginning of lugolization.

† Initial B.M.R. and lowest B.M.R. after lugolization or thyroidectomy.

pathological galactosurias ranging between 3 and 12.5 grams were encountered. In six cases (8, 9, 10, 11, 12, 13—tables 2 and 3) the influence of iodine and thyroidectomy was noted. The data are too meager to permit any conclusion, except that there is a definite tendency for the galactose tolerance test to improve with the iodine therapy and consequent decrease of the basal metabolic rate. Cases 8, 9 and 11 illustrate the definite beneficial effect of thyroidectomy, i.e., the return to normal galactose tolerance. In case 10 there was a postoperative increase in the galactosuria and basal rate. The clinical results in this case also indicated that thyroidectomy was fol-

* In the author's new technic⁹⁶ for the estimation of galactose tolerance the sugar content of each fraction is determined before and after fermentation. The non-fermentable fraction is galactose. A correction is made for the galactose which may have disappeared from the mixture as determined in a galactose control. The fermented fraction then represents the glucose concentration present with the galactose. When fermentation is permitted to continue over a period of 24 hours, amounts varying between 0.1 and 0.7 per cent (0.3 per cent in the majority) of reducing substance was found to disappear in the process of fermentation. If a galactose solution is treated with a yeast suspension for one hour, at temperatures varying between 40 to 45° C., amounts up to 0.13 per cent may disappear. After 24 hours, as much as 0.38 per cent may disappear. In the author's technic, therefore, fermentation is carried on for one hour at the above temperature and the correction for disappearance of galactose by diffusion into the yeast cells is made from a galactose control.

lowed by a hyperthyroid reaction. Case 12 demonstrated return to normal galactose tolerance with lugolization. Cases 9 and 10 (table 2) confirm an observation made by Bartels, with the hippuric acid test, that normal function may not return after thyroidectomy for varying periods of time. In case 9 the liver function was still impaired on the fourth day after operation. By the tenth day it had returned to normal. In case 10 a determination made on the fourth day was abnormally high. In case 11, normal function had already returned on the fourth day postoperative.

TABLE II

The Influence of Iodine Therapy and Thyroidectomy on Pathological Galactosuria

Case No.	Age	Sex	Weight Loss Lbs.	Duration of Disease Months	B.M.R. Per Cent	Grams Galactosuria	
						Pre-operative	Post-operative
8. J. S.	42	F	15	6	+34-18*	5.4	0.68
9. R. F.	38	F	50	12	+79-36	3.0 4.2	3.48 (4th day) 2.0 (10th day)
10. S. H.	50	M	45	9	+48-20	6.8† 5.2 3.8	5.9 (4th day)
11. E. L.	42	F	10	5	+63-20	4.7 6.1† 3.9	2.2 (4th day)
12. E. H.	41	F	15	36	+37-17	4.0 1.2	
Average	43		25	14	+52-22		

* Maximum B.M.R. before and minimum B.M.R. after iodine (Lugol's sol.).

† Galactose tolerance tests performed at intervals during iodine treatment.

‡ At height of upper respiratory infection.

In the group of cases with normal galactose tolerance, the average age of the subjects was approximately a decade lower than that of the group with pathological galactosuria; the weight loss in the former group averaged six pounds less. The duration of the disease was nine months less in this group. The initial basal metabolic rate was, on the average, 12 per cent greater in the cases with abnormal galactose tolerance. It is significant that case 1 of the normal group had been treated with iodine before admission to the hospital and was in a remission stage, and that case 2 of this group had previously undergone a first stage thyroidectomy. The results of the galactose test appeared to correlate more uniformly than any other test with the clinical criteria of severity of the disease such as increased weight loss, duration of disease, and basal rate.

Of importance are the observations of the effect of infections on the galactose tolerance in the course of thyrotoxic disease (cases 11, 13—table

3). In case 11 a simple afebrile upper respiratory infection was accompanied by a rise in galactose excretion from 4.7 to 6.1 grams in spite of the fact that Lugol's solution was being administered. A corresponding rise in the basal metabolic rate also occurred. In case 13, during the development of a furuncle in the external auditory canal without fever, the excretion of galactose rose from 2 grams to 12.5 grams during the infection and then fell to 3.8 grams after subsidence of the infection. During the afebrile infection the basal metabolic rate rose from 33 to 41 per cent and subsequently dropped to 14 per cent.

TABLE III
The Effect of Infection on Galactosuria in Hyperthyroidism

Case No.	Basal Metabolic Rate			Galactosuria, Grams		
	Before	Infection	After	Before	Infection	After
11. E. L.	+20	42*	43	4.7	6.1	3.9
13. E. S.	+33	41†	14	2	12.7	3.8

* Upper respiratory infection. No fever.

† Furuncle of external auditory canal. Afebrile.

The special technic of performing the galactose test proved that the sugar excreted in the urine was essentially galactose. Carefully controlled yeast fermentation of a standard galactose solution, simultaneously with the test urines, disclosed the disappearance of small amounts of this sugar by means of adsorption and diffusion into the yeast cells. Yeast fermentation of test fractions without a galactose control might lead to the erroneous impression that the sugar which disappeared during the fermentation process was necessarily glucose.

COMMENT

There can be no question that the liver is frequently damaged in thyrotoxicosis. The accumulated data indicate that pathological changes may occur in the liver independent of those of chronic passive congestion due to heart failure. These changes may vary from simple acute fatty degenerative and necrotic lesions to a chronic form of atrophy and cirrhosis. On a pathological basis alone, one would expect abnormal results with the clinical liver function tests. In some cases certain tests may indicate no functional impairment and there may be only slight impairment even with the sensitive cinchophen oxidation and hippuric acid synthesis tests. In other cases all the tests indicate a slight to moderate functional impairment. Severe functional impairment is the exception, yet from the pathological lesions in severe cases of hyperthyroidism one would expect drastic functional changes. Discrepancies between the pathological lesions in the liver and the results of liver function tests occur as they do also in patients with heart failure. In heart failure, the cases exhibiting jaundice do not necessarily show the most

severe hepatic lesions (Kugel and Lichtman).⁹⁷ In some cases of Graves' disease jaundice may occur independently of the functional disturbances and is dependent upon a superimposed cholangitis or hepatitis (catarrhal jaundice). The instances of true acute yellow atrophy directly attributable to the thyrotoxic state are extremely rare. Considering the relative frequency of hyperthyroidism in the medical wards of a general hospital the incidence of jaundice in these cases is relatively uncommon. It occurred only in 8 per cent of our fatal cases.

The basic functional disturbance in the liver appears to be associated with carbohydrate metabolism. The data, however, indicate that it is not the glycogen depletion in the liver alone which is responsible for the abnormal liver function tests. There are actual anatomical changes in the liver cells. Toxic necrosis has also been described in the heart muscle and other tissues in this disease. Liver function tends to improve promptly with the administration of Lugol's solution, intravenous glucose therapy, and partial or total removal of the thyroid gland. Although the changes in the liver in some cases progress to chronic fibrotic disease, liver function appears to improve promptly after alleviation of the thyrotoxicosis by iodine administration or thyroidectomy.

The exact mechanism of the functional derangement of the liver is not established, but the following hypothesis may be advanced. The glycogen depletion in the liver is a physiological manifestation of the metabolic demands of the hyperthyroid state. The carbohydrate stores are exhausted and the protein stores also drawn upon for their carbohydrate fraction. This in itself should not produce liver function disturbance. However, glycogen exhaustion and protein depletion deprive the liver of its prime protective agents against poisons. The unprotected liver cell then may become vulnerable to thyroxine, products of endogenous intermediary metabolism or bacterial toxins from the intestinal tract or other foci in the body. The anatomical changes in the liver are produced by the action of these toxic elements.

The author's modification of the technic of estimating galactose in the test urines yielded the fact that sugar excreted in the urine during the test in this endocrine disorder is mainly galactose. The galactose test thus may be applied to the study of liver functions in endocrine disorders provided the excreted sugar in each instance is checked by yeast fermentation.

It is a common clinical observation that patients with hyperthyroidism tolerate upper respiratory and other infections poorly. The galactose test indicates that these infections further compromise the function of the liver even in the absence of fever. The damaging effect of infection on liver function has been reported elsewhere in other diseases such as tuberculosis (Steidl and Heise, 1935).⁹⁸

SUMMARY

A review of the facts reported in the literature and personal studies of liver function in patients with hyperthyroidism indicate that the liver is

frequently damaged, functionally and anatomically, in this disease. The anatomical changes are sometimes severe enough to produce functional changes. The changes may be regarded as representing varying degrees of reaction of this organ to the thyroid derangement. The following facts appear to have been established:

1. Employing various clinical liver function tests, 45 to 90 per cent of all cases of hyperthyroidism show some functional impairment, usually of slight to moderate degree. The cinchophen oxidation, the hippuric acid synthesis, and the galactose tolerance tests constitute the best measures for evaluating liver function in this disease. The galactose tolerance test appears to give results which may be more uniformly correlated with clinical criteria of severity of thyrotoxicosis, such as weight loss, duration of the disease, and basal metabolic rate. Other tests show either no correlation or only partial correlation with these criteria.

2. Factors which may directly improve impaired liver function are the administration of iodine and partial or total thyroidectomy. Normal function may be restored.

3. Upper respiratory infections (coryza) and other infections may aggravate existent liver function disturbance even in the absence of fever.

4. The sugar which appears in the urine following oral administration of galactose is mainly galactose.

5. The occurrence of jaundice in patients with thyrotoxicosis may be completely unrelated to the underlying hyperthyroid state and depend on intercurrent cholangitis, catarrhal jaundice or gall stones.

6. When jaundice is definitely determined by the thyrotoxicosis, it usually occurs in the severe cases.

7. There appears to be an increased degree of impaired liver function in thyroid crisis but there is no evidence to indicate that impaired liver function is the prime inciting agent in thyroid crisis.

A mechanism for the hepatic functional derangement in hyperthyroidism is suggested: The depletion of glycogen in the liver in this disease deprives the liver of its prime protective factor against poisons and establishes conditions conducive to damage by toxic agents, such as thyroxine, endogenous metabolic products, or bacterial toxins derived from the bowel or foci elsewhere in the body.

BIBLIOGRAPHY

1. GAUNT, R., REMINGTON, J. W., and EDELMANN, A.: Effect of progesterone and other hormones on liver glycogen, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 429.
2. BRITTON, S. W., and SILVETTE, H.: Effects of cortico-adrenal extract on carbohydrate metabolism in normal animals, *Am. Jr. Physiol.*, 1932, c, 693-700.
3. LONG, C. N. H., and KATZIN, B.: Effect of adrenal cortical hormone on carbohydrate stores of fasted hypophysectomized rats, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 516-518.
4. FARRANT, R.: Hyperthyroidism: its experimental production in animals, *Brit. Med. Jr.*, 1913, ii, 1363-1367.

5. CRAMER, W., and KRAUSE, R. A.: Carbohydrate metabolism and its relation to the thyroid gland, *Proc. Roy. Soc. Med., London*, 1913, lxxxvi, B, 550-560.
6. PARHON, M.: Sur la teneur en glycogène du foie et des muscles chez les animaux traités par des préparations thyroïdiennes, *Jr. de physiol. et de path. gén.*, 1913, xv, 75-78.
7. KURIYAMA, S.: The influence of thyroid feeding upon carbohydrate metabolism, *Am. Jr. Physiol.*, 1917, xliii, 481-496. The influence of thyroid feeding upon carbohydrate metabolism. 1. The storage and mobilization of the liver glycogen in thyroid-fed animals, *Jr. Biol. Chem.*, 1918, xxxiii, 193-205.
8. ABELIN, J., and JAFFE, J.: Ueber den Einfluss der proteinogenen Amine, Phenyl und p-Oxyphenyläthylamin auf den Kohlenhydratstoffwechsel der Leber, *Biochem. Ztschr.*, 1920, cii, 39-57.
9. ROMEIS, B.: Ueber die Wirkung des Thyroxins auf Körpergewicht und Leberglykogen weisser Mäuse, *Biochem. Ztschr.*, 1923, cxxxv, 85-106.
10. FUKUI, T.: Ueber den Kohlenhydratverlust der Leber hyperthyroidisierter Ratten. Zugleich ein Beitrag zur Frage der Werthbestimmung von Schilddrüsenpräparaten, *Arch. f. d. ges. Physiol.*, 1925, ccx, 410-431.
11. BOESL, O.: Ueber die Einwirkung von Thyroxin auf den Glykogengehalt des Skelettmuskels und der Leber bei Meerschweinchen, *Biochem. Ztschr.*, 1928, ccii, 299-319.
12. ABDERHALDEN, E., and WERTHEIMER, E.: Studien ueber die Wirkung des Thyroxins auf den tierischen Organismus und ins besondere auf die Wärmeregulation des Gleichwarmblüters, *Arch. f. d. ges. Physiol.*, 1928, ccxix, 588-608.
13. ABELIN, I., and SPICHTIN, W.: Ueber den Einfluss der Schilddrüsensubstanzen auf den Gesamtkreatiningehalt der Leber und des Muskels, *Biochem. Ztschr.*, 1930, cxxxviii, 250-256.
14. LAWRENCE, R. D., and McCANCE, R. A.: The effect of starvation, phloridzin, thyroid, adrenaline, insulin and pituitrin on the distribution of glycogen in the rat, *Biochem. Jr.*, 1931, xxv, 570-578.
15. KNITTEL, G.: Ueber die Beeinflussung des Leberglykogens unter Thyroxinwirkung stehender Tiere durch Zucker-Insulin-gaben, *Ztschr. f. d. ges. exper. Med.*, 1931, lxxvi, 362-368.
16. ALTHAUSEN, T. L., and THOENES, E.: Influence on carbohydrate metabolism of experimentally induced hepatic changes; fasting with administration of thyroxine, *Arch. Int. Med.*, 1932, i, 46-57.
17. COGGESHALL, H. C., and GREENE, J. A.: Influence of desiccated thyroid gland, thyroxin and inorganic iodine upon storage of glycogen in liver of albino rat under controlled conditions, *Am. Jr. Physiol.*, 1933, cv, 103-109.
18. FRAZIER, W. D., and FRIEMAN, H.: Alterations in liver glycogen following thyroid, iodine, and glucose feeding, *Surg., Gynec., and Obst.*, 1935, lx, 27-29.
19. HIMMELBERGER, L. R.: Thyroid hormone in blood and urine in Graves' disease: preliminary paper, *Endocrinology*, 1931, xi, 264-266.
20. EITEL, H., LOEHR, G., and LOESER, A.: Untersuchungen ueber die Stoffwechselwirkungen der thyreotropen Substanz des Hypophysenvorderlappens, *Klin. Wchnschr.*, 1933, xii, 1776-1777.
21. WILDER, R. M., and SANSUM, W. D.: d-Glucose tolerance in health and disease, *Arch. Int. Med.*, 1917, xix, 311-335.
22. REINWEIN, H., and SINGER, W.: Studien über Gewebsatmung. IV. Mitteilung. Der Einfluss von Thyroxins, Adrenalin und Insulin auf den Sauerstoffverbrauch überlebender Leberzellen, *Biochem. Ztschr.*, 1928, cxcviii, 152-159.
23. DRESEL, K., GOLDNER, M., and HIMMELWEIT, F.: Zum Basedowproblem, *Deutsch. med. Wchnschr.*, 1924, lv, 259-261.
24. SCHRYVER, S. B.: Researches on the autolytic degradation of tissue. Part II. On the influence of the thyroid on autolysis, *Jr. Physiol.*, 1905, xxxii, 159-170.
25. HIGGINS, G. M.: Experimental pathology of the liver. XII. Effects of feeding desiccated thyroid gland on restoration of the liver, *Arch. Path.*, 1933, xvi, 226-231.

26. SIMONDS, J. P., and BRANDEIS, W. W.: Effect of experimental hyperthyroidism and of inanition on the heart, liver and kidneys, *Arch. Path.*, 1930, ix, 445-460.
27. HOSKINS, E. R.: The growth of the body and organs of the albino rat as affected by feeding various ductless glands (thyroid-thymus, hypophysis and pineal), *Jr. Exper. Zoöl.*, 1916, xxi, 295-346.
28. HEWITT, J. A.: The effect of administration of small amounts of thyroid gland on the size and weight of certain organs in the male white rat, *Quart. Jr. Exper. Physiol.*, 1919-1920, xii, 347-354.
29. ZAVADOVSKY, B., and PERELMUTTER, Z. M.: Ueber das Schicksal des Thyroxins im Blute und in den Geweben der hyperthyreoidisierten Hühner, *Arch. f. Entwcklungsmechn. d. Organ.*, 1927, cix, 210-237.
30. BLUM, F., and GRUTZNER, R.: Studien zur Physiologie der Schilddrüse, *Ztschr. f. physiol. Chem.*, 1920, cx, 277-297.
31. KENDALL, E. C.: The physiologic action of thyroxin, *Endocrinology*, 1919, iii, 156-163.
32. KRAYER, O.: Ueber Verteilung und Ausscheidung des Jodes nach Zufuhr von Schilddrüsenstoffen, *Arch. f. exper. Path. u. Pharmacol.*, 1928, cxxviii, 116-125.
33. LEITES, S., and ISABOLINSKAJA, R.: Veraenderungen in Gallenchemismus und Sekretion unter dem Einfluss des Thyroxins, *Klin. Wchnschr.*, 1933, xii, 149-150.
34. BESUGLOW, V. P., and TUTKEWITSCH, L. M.: Die Schilddrüse und ihr Einfluss auf die Gallensekretion und auf den Gehalt der Galle an Cholesterin, *Ztschr. f. d. ges. exper. Med.*, 1933, lxxxvii, 52-57.
35. PARHON, C. I., and WERNER, G.: Sur la teneur en cholesterol de la bile, de la peau, et des organes chez les animaux soumis au traitement thyroïdien, *Compt.-rend. Soc. de biol.*, 1931, cvii, 401.
36. JOHNSON, J., and RIEGEL, C.: The effect of experimental hyperthyroidism and hypothyroidism upon the concentration of cholesterol in hepatic bile, *Surgery*, 1939, v, 260-266.
37. HASHIMOTO, H.: Heart in exophthalmic hyperthyroidism with special reference to the histology, *Endocrinology*, 1921, v, 579-606.
38. GERLEI, F.: Necrose du foie consecutive a l'empoisonnement par la thyroxine, *Ann. d'anat. path.*, 1933, x, 555-560.
39. DAVIS, N. C., and WHIPPLE, G. H.: The influence of fasting and various diets on the liver injury effected by chloroform anesthesia, *Arch. Int. Med.*, 1919, xxiii, 612-654.
40. CAMERON, G. R., and KARUNARATNE, W. A. E.: Liver changes in exophthalmic goiter, *Jr. Path. and Bact.*, 1935, xli, 267-282.
41. WELLER, C. V.: Hepatic pathology in exophthalmic goiter, *ANN. INT. MED.*, 1932-1933, vii, 543-560.
42. HABAN, G.: Ueber die Leberveraenderungen bei Morbus Basedowii mit besonderer Berücksichtigung der Lebercirrhose, *Beitr. z. path. Anat. u. z. allg. Path.*, 1933, xcii, 88-100.
43. BEAVER, D. C., and PEMBERTON, J. DE J.: The pathological anatomy of the liver in exophthalmic goiter, *ANN. INT. MED.*, 1933, vii, 687-708.
44. RÖSSLE, R.: Über die Veränderungen der Leber bei der Basedowsche Krankheit und ihre Bedeutung für Entstehung anderer Organsklerosen, *Virchow's Arch. f. path. Anat.*, 1933, ccxci, 1-46.
45. ZELDENRUST, J., and BECK, C. C. VAN: Morphological and experimental contribution to pathogenesis of hepatic changes in exophthalmic goiter, *Nederl. Tijdschr. v. Geneesk.*, 1939, lxxxiii, 1114-1125.
46. PETTAVEL, C. A.: Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1914, xxvii, 694-749.
47. WEGELIN: Handbuch der speziellen pathologischen Anatomie u. Histologie, Henke u. Lubarsch, 1926, Julius Springer, Berlin.
48. PAUL: Zur Basedow'schen Krankheit, *Berl. klin. Wchnschr.*, 1865, ii, 277-282.

49. TROUSSEAU: Lectures on clinical medicine, New Sydenham Society Translation, London, 1868, i, 570.
50. FARNER, E.: Beiträge zur pathologischen Anatomie des Morbus Basedowi mit besonderen Berücksichtigung der Struma, Arch. f. path. Anat., 1896, cxliii, 509-574.
51. ASKANAZY, M.: Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung, Deutsch. Arch. f. klin. Med., 1898, lxi, 118-186.
52. DINKLER: Über den klinischen Verlauf und die pathologisch-anatomischen Veränderungen eines schweren durch Hemiplegie, bulbäre und psychische Störungen ausgezeichneten Falles von Basedowscher Krankheit, Arch. f. Psychiat., 1900, xxxiii, 335-365.
53. MARINE, D., and LENHART, C. H.: Pathological anatomy of exophthalmic goiter; heart disease; jaundice; death, Arch. Int. Med., 1911, viii, 265-316.
54. LANDAU: Die pathologische Histologie der Basedowstruma, München. med. Wchnschr., 1911, lviii, 1213.
55. PETTAVEL, C. A.: Beitrag zur pathologischen Anatomie des Morbus Basedow, Deutsch. Ztschr. f. Chir., 1912, cxvi, 488-543.
56. RAUTMANN, H.: Pathologisch-anatomische Untersuchungen über die Basedowsche Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1915, xxviii, 489-618.
57. HOLST, J.: Untersuchungen über die Pathogenese des Morbus Basedowii (der thyreosen), Supp. IV, Acta chir. Scandin., 1923, P. A. Norstedt and Sons, Stockholm and Kristiania, p. 212.
58. BARTELS, E. C.: Liver function in hyperthyroidism as determined by the hippuric acid test, ANN. INT. MED., 1938, xii, 652-674.
59. BOYD, E.: Normal variability in weight of the adult human liver and spleen, Arch. Path., 1933, xvi, 350-372.
60. HABERSHON, S. O.: Exophthalmic goiter, heart disease; jaundice; death, Lancet, 1874, 1, 510.
61. EGER: Beitrag zur Pathologie des Morbus Basedowii, Deutsch. med. Wchnschr., 1880, vi, 153-157.
62. GAILL: Die Basedowsche Krankheit, Diss. München, 1883.
63. STRÜMPPELL: Lehrbuch der speciellen Pathologie und Therapie der inneren Krankheiten, 3rd ed., 1886, Wm. Engelmann, Leipzig, ii, Part I, 138.
64. BURTON, F. W.: Pigmentation and other cutaneous affections in Graves' disease, Lancet, 1888, ii, 573-574.
65. WESTEDT, W.: Sechs Fälle von Morbus Basedowii, Diss. Kiel, 1889.
66. BOINET, and BOURDILLON: Quelques phénomènes peu communs dans le goitre exophthalmique, Marseille méd., 1891, xxviii, 606-609.
67. MOEBIUS: Die Basedow'sche Krankheit, A. Hoelder, Vienna, 1896, p. 48.
68. SUTCLIFF, E. H.: An extraordinary acute case of Graves' disease, Lancet, 1898, 1, 717.
69. DIEULAFOY, G.: Quoted by Eder.⁸⁰
70. SATTLER, T.: Die Basedowsche Krankheiten, Graefe Saemisch's Handbuch der gesamten Augenheilkund, 2nd ed., 1906, Wm. Engelmann, Leipzig, 9, Pt. 2.
71. CHVOSTEK, F.: Morbus Basedowi und die Hyperthyreosen, 1917, Julius Springer, Berlin.
72. CROTTI, A.: Thyroid and thymus, 1922, Lea and Febiger, Philadelphia.
73. BOOTHBY, W. M.: Part 4. Diagnosis and treatment of diseases of the thyroid gland, 1922, Oxford Univ. Press, N. Y., p. 111.
74. KLOSE, H.: Die Chirurgie der Basedowschen Krankheit in von Brun's neue Deutsch. Chirurgie, Stuttgart, 1929, xlv, 371.
75. BARKER, L. F.: Thyreo-intoxication with necrosis and atrophy of liver, damage to the heart muscle and kidneys and terminal broncho-pneumonia, Med. Clin. N. Am., 1930, xiv, 261-263.
76. ASSMANN, H.: Leber und Milz bei Morbus Basedow, München. med. Wchnschr., 1931, lxxviii, 221-225.

77. HEILMEYER, L.: Blutfarbstoffwechselstudien. 3 Mitteilung: Blutmauserung und Leberfunktion beim Morbus Basedow, *Deutsch. Arch. f. klin. Med.*, 1931, clxxi, 515-528.
78. LICHTMAN, S. S.: Liver function in hyperthyroidism, *Arch. Int. Med.*, 1932, i, 721-729.
79. RETZLAFF, L.: Hepatic involvement in exophthalmic goiter, *Ztschr. f. klin. Med.*, 1937, cxxxii, 423-576.
80. EDER, M. D.: Three cases of jaundice occurring in persons suffering from exophthalmic goiter, *Lancet*, 1906, i, 1758.
81. HIROSE, M.: Über die alimentäre Galactosurie bei Leberkrankheiten und Neurosen, *Deutsch. med. Wchnschr.*, 1912, xxxviii, 1414-1416.
82. STRAUSS, H.: Über neurogene und thyreogene Galaktosuria, *Neurol. Centralbl.*, 1913, xxxii, 1281-1284.
83. SANGER, B. L., and HUN, E. G.: Glucose mobilization rate in hyperthyroidism, *Arch. Int. Med.*, 1922, xxx, 397-406.
84. KUGELMANN, B.: Über Störungen im Kohlehydratstoffwechsel beim Morbus Basedow, *Klin. Wchnschr.*, 1930, ix, 1533-1534.
85. ADLER, A., and LEMMEL, H.: Zur feineren Diagnostik der Leberkrankheiten: Cholesterin und Cholesterin-ester im Blute Leberkranken, *Deutsch. Arch. f. klin. Med.*, 1928, clviii, 173-213.
86. DRESEL, K., and GOLDNER, M.: Ein neuer biologischer Test für Schilddrüsenstoffe, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 1929, xli, 534.
87. WILLIS, D. A., and MORA, J. M.: Biological reaction for hyperthyroidism, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 562-563.
88. EILBOTT, W.: Funktionsprüfung der Leber mittel Bilirubinbelastung, *Ztschr. f. klin. Med.*, 1927, cvi, 529-560.
- BERGMANN, G.: Zur funktionellen Pathologie der Leber insbesondere der Alkohol-aetiologie der Cirrhose, *Klin. Wchnschr.*, 1927, vi, 776-780.
89. MADDOCK, W. G., COLLIER, F. A., and PEDERSEN, S.: Thyroid crisis: its relationship to liver function and adrenalin, *West. Jr. Surg.*, 1936, xlv, 513-521.
90. FOSS, H. L., HUNT, H. F., and McMILLAN, R. M.: The pathogenesis of crisis and death in hyperthyroidism, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1090-1094.
91. RAGINS, A. B.: Value of Takata and Ara reaction as diagnostic and prognostic aid in cirrhosis of the liver, *Jr. Lab. and Clin. Med.*, 1935, xx, 902-913.
92. MADDEN, S. C., WINSLOW, P. M., HOWLAND, J. W., and WHIPPLE, G. H.: Blood plasma protein regeneration as influenced by infection, digestive disturbances, thyroid and food proteins, *Jr. Exper. Med.*, 1937, lxxv, 431-454.
93. ALTHAUSEN, T. K., and THOENES, E.: Influence of carbohydrate metabolism of experimentally induced hepatic changes, *Arch. Int. Med.*, 1932, i, 46-47.
94. ALTHAUSEN, T. L., and WEVER, G. K.: Galactose tolerance in hyperthyroidism, *Jr. Clin. Invest.*, 1937, xvi, 257-259.
95. ALTHAUSEN, T. L.: A test for intestinal absorption, *Am. Jr. Digest. Dis. and Nutr.*, 1939, vi, 544-548.
96. LICHTMAN, S. S.: Modification of the galactose tolerance test based on the differential fermentation of the glucose occurring with galactose in the urine, *Jr. Lab. and Clin. Med.*, 1940, xxv, 1193-1198.
97. KUGEL, M. A., and LICHTMAN, S. S.: Factors causing clinical jaundice in heart disease, *Arch. Int. Med.*, 1933, lii, 16-29.
98. STEIDL, J. H., and HEISE, F. H.: Hepatic function in pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1935, xxxii, 677-683.

LARGE HEALED TUBERCULOUS FOCUS (PROBABLY PRIMARY) SIMULATING METASTATIC CARCINOMA OF THE LUNG *

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KNOWLEDGE of the primary tuberculous complex dates from the work of Kuss (1898), Albrecht (1909), and Ghon (1912).† The pulmonary component of the complex, which is a zone of caseous pneumonia surrounding the site of the initial infection, is known in modern medicine as the primary or Ghon focus (tubercle). It is usually located subpleurally and is often very small, generally not larger than a bean, rarely larger than a hazel-nut. Over 95 per cent of cases have only one focus, and cases having more than two are very rare. It is most often found in the lower portion of the upper lobe or the upper portion of the lower. The right lung is somewhat more frequently involved than the left, and the upper lobes more often than the lower.^{3, 9}

Roentgenographically, the focus is described by Köhler⁶ as ranging in size from that of a hempseed to that of a pea, never seen in the apices, hilar region, or the middle of the lungs, but almost invariably in the lateral part of the lungs, not far removed from the lateral wall of the thorax; it is encountered at a level of from the second to the sixth intercostal spaces. Bigler¹ states that the ordinary primary lesion may not show on the roentgen film unless it is 1 to 1.5 cm. in diameter, is near the lateral wall of the chest and not behind the diaphragmatic shadow, is surrounded by a definite area of atelectasis, or contains calcium.

Wallgren¹¹ has recently made an important contribution by following cases of childhood tuberculosis for a considerable number of years. Most primary lesions heal by fibrosis without calcification and the resulting scar is rarely visible roentgenographically. In the remaining cases, healing is by fibrosis with calcification. At least several years are required before calcification progresses to the point of radio-opacity. Wallgren has observed cases where the resulting calcified focus grew smaller and denser over a period of years due to the contraction of connective tissue and compaction of the lime. Then, in some, the lime began to absorb; decreased density thus resulted. Myers⁸ and his co-workers have carried out similar studies. Initial lesions were observed to last from several months to a year or more, then to disappear, and subsequently become replaced by calcified shadows. In a series of 34 cases with enlarged hilar nodes, no visible parenchymal lesion, and a positive tuberculin reaction, 12 developed calcified Ghon foci after a lapse of several years.

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† Fried² has recently written a historical review on the primary tuberculous complex.

When seen in children these lesions usually present no serious diagnostic difficulties. During adult life, however, the failure to interpret properly such shadows may lead to errors in diagnosis. The following is a report of four cases in all of which, because of peculiar circumstances in their clinical course, large dense shadows were at first incorrectly interpreted as neoplastic metastases when in reality they were large healed tuberculous (probably primary) foci.

CASE REPORTS

Case 1. E. L., male, aged 65, was admitted to Beth Israel Hospital in March 1932, complaining of abdominal pain, constipation, loss of appetite, and recent weight loss. Diabetes had been detected elsewhere a short time prior to admission.

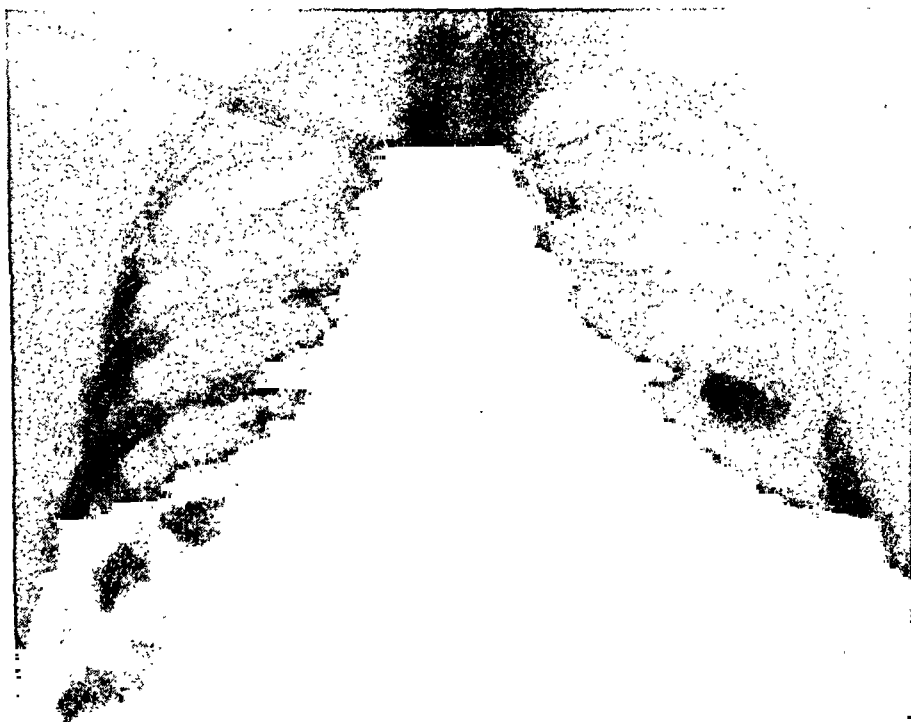


FIG. 1. *Case 1.* Roentgenogram showing shadow in the lower left lung field, first thought to be a metastasis from a carcinoma of the colon, actually a healed tuberculous focus.

On physical examination, the salient abnormal findings were confined to the cardiovascular system and to the abdomen, where a palpable mass was noted in the right upper quadrant. Laboratory studies, aside from the evidence of diabetes, showed nothing remarkable.

Satisfactory roentgen studies of the colon could not be carried out. A roentgenogram of the chest (figure 1) showed cardiac enlargement, and a round, dense, sharply circumscribed shadow in the lower left lung field. This was interpreted as a metastasis, probably from a carcinoma of the ascending colon.

The patient improved for a time and then symptoms of circulatory insufficiency appeared. The picture was further complicated by the development of cerebral symptoms, which were interpreted as being due to intracranial metastases. He died six weeks after admission.

Postmortem examination revealed severe occlusive changes in the coronary arteries with resultant myocardial damage. There was a large uriniferous cyst in the upper pole of the right kidney. In the lower portion of the left upper lobe of the lung a healed tuberculous focus measuring 3.2 cm. in diameter was found (figure 2).



FIG. 2. Case 1. Mass from lower lobe of left lung corresponding to shadow in figure 1. Note concentric ring-like arrangement, and the normal appearance of the surrounding lung tissue. This is most likely a healed tuberculous (probably primary) lesion. (Actual size.)

Grossly, this appeared to consist chiefly of whitish, firm tissue arranged in concentric rings. On microscopic examination, the same arrangement was seen, the layers consisting of hyalinized connective tissue, with occasional infiltration of lime salts. No cellular structure or ossification was seen although numerous sections were examined. The surrounding pulmonary tissue appeared perfectly normal.

Comment: The combination of gastrointestinal complaints, abdominal mass, and round shadow in the lung led to the erroneous diagnosis of carcinoma of the colon with a pulmonary metastasis. As the necropsy showed, the mass was a uriniferous cyst and the pulmonary shadow represented a healed, probably primary, tuberculous focus (see below).

Case 2. M. K., male, aged 25, entered Beth Israel Hospital on August 5, 1930. Aside from a "cigarette cough" of many years' duration, he was perfectly well until five weeks prior to admission, when he suddenly became short of breath and expectorated a small amount of bloody sputum. The following day he had a chill which was followed by fever and expectoration of rusty sputum. A physician diagnosed pneumonia and treated him for the next two weeks, during which time the fever disappeared and the other symptoms diminished in intensity. One week later the fever recurred, and during the two week period preceding admission his temperature was intermittently elevated and there was expectoration of bloody foul sputum. The day before he entered the hospital he had a large hemoptysis.

On examination the temperature was 104° F. He was dyspneic and orthopneic and was expectorating large amounts of foul blood-tinged sputum. Over the lower

half of the left chest, there was impaired resonance, broncho-vesicular breathing, and moist râles.

A roentgenogram of the chest (figure 3) showed a large rounded mass in the lower left lung adjacent to the cardiac border. In the right midlung field a smaller, round, sharply circumscribed shadow was seen. The interpretation was a carcinoma of the left lung with secondary suppuration, and a metastasis to the right lung.

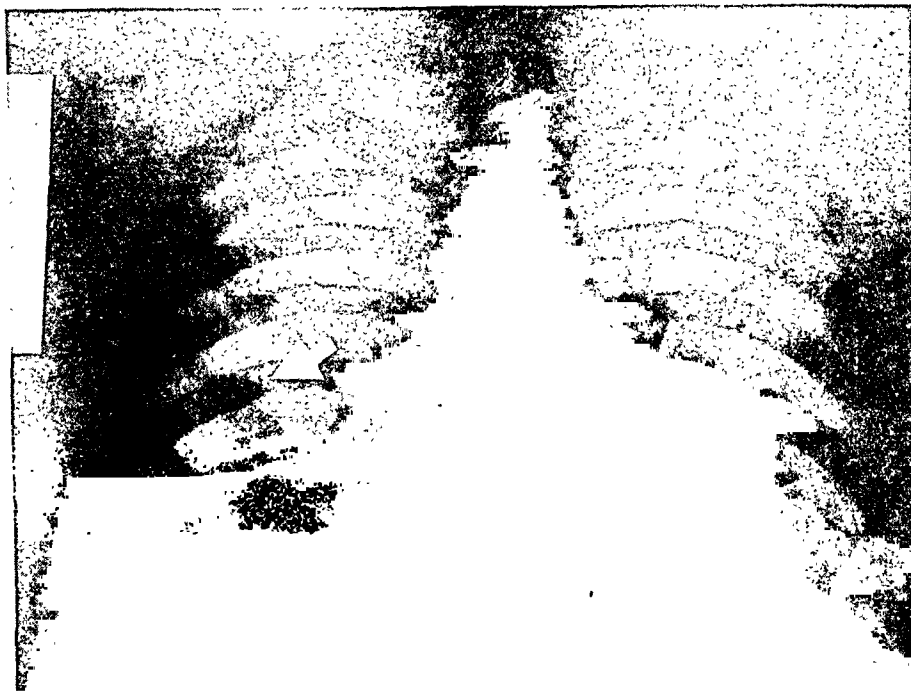


FIG. 3. *Case 2.* Roentgenogram on admission, showing paracardiac shadow in left lung due to abscess but first thought carcinoma. The shadow in the right lung (arrow) was first thought to be a carcinomatous metastasis.

After four days the temperature fell to normal and remained so thereafter. The expectoration diminished in volume and was no longer bloody or foul. Bronchoscopy on the twentieth day showed no abnormalities except for an odorless muco-purulent secretion from several branches of the left lower lobe bronchus. Roentgenograms of the chest showed gradual diminution in size of the shadow in the left lung; on the last two films there was cavity formation behind the heart shadow. The lesion on the right side remained unchanged.

The patient was discharged after a month and during a stay in the country made an uneventful recovery. When seen two and a half years later, he stated that he had remained free of symptoms. A roentgenogram of the chest (figure 4) showed no abnormalities other than the shadow in the right lung noted previously; this had not changed in size or density.

Comment: The clinical course indicated that the shadow in the left lung was due to a pulmonary abscess which later healed spontaneously, and not to a carcinoma as originally thought. The smaller shadow in the right lung, at first considered metastatic, failed to change in appearance in two and a half years and must therefore be regarded as a healed tuberculous focus, unrelated to the condition which brought the patient to the hospital.

Case 3. S. S., male, aged 55, came to the out-patient department of Beth Israel Hospital in September 1931. He had been treated by his physician for many years for a peptic ulcer but his symptoms had recently become more severe and had changed in character. Physical examination showed slight tenderness in the epigastrium and in the right upper quadrant but was otherwise negative.

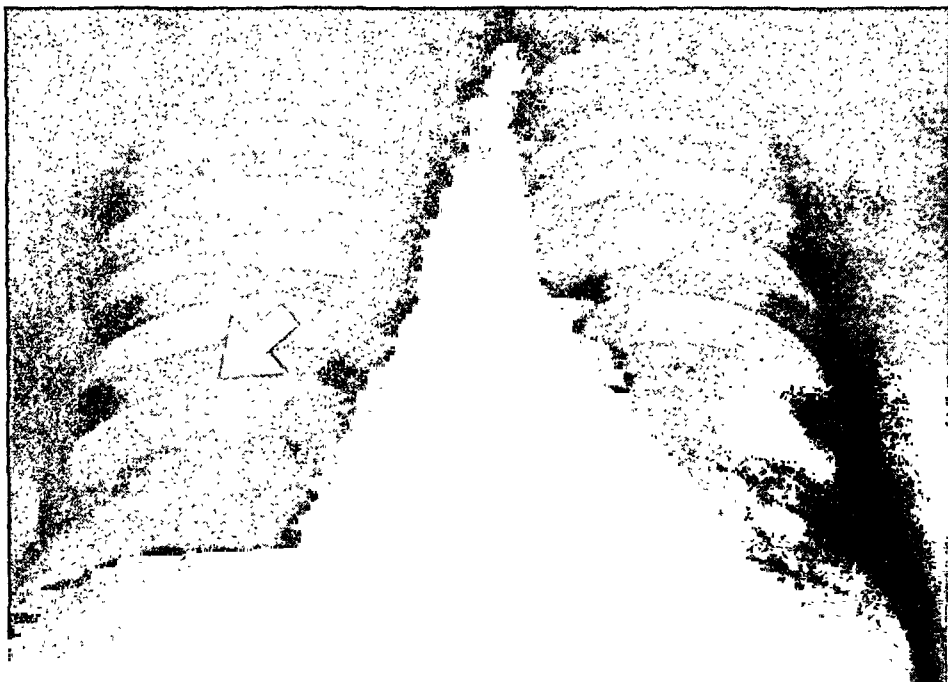


FIG. 4. *Case 2*, two and one-half years later. Note complete disappearance of abnormal shadow on left, while that in right lung (arrow) is unchanged.

Roentgen studies of the gastrointestinal tract showed an irregularity in the outline of the pylorus suggesting carcinoma. A roentgenogram of the chest (figure 5) showed a circular lesion about 2 cm. in diameter at the base of the right lung. This was regarded by the roentgenologist as probably a Ghon focus, but because of the gastrointestinal findings metastatic carcinoma was considered.

Operation was advised but the patient refused. He was placed on a Sippy regime and improved considerably. Because of a recurrence of symptoms 15 months later, new roentgen studies were made. Examination of the gastrointestinal tract showed the changes of a duodenal ulcer with periduodenal adhesions. In retrospect, the irregularity of the pyloric outline seen in the previous series which led to the suspicion of carcinoma was probably also due to adhesions. A roentgenogram of the chest showed the lesion previously noted to be unchanged in appearance.

Comment: As in case 1, the combination of symptoms and roentgen findings suggestive of disease of the gastrointestinal tract with the additional finding of a circular shadow at the base of the lung led to the erroneous diagnosis of carcinoma with a pulmonary metastasis. The benign clinical course over a period of 15 months served to rule out carcinoma.

The unchanged appearance of the pulmonary lesion during this time indicated that this was a healed tuberculous focus.

Case 4. B. G., female, aged 53, appeared in the out-patient department of Beth Israel Hospital in March 1933, complaining of severe sticking pains in the left side



FIG. 5. *Case 3.* Roentgenogram showing dense shadow in right lower lung field, first considered a possible metastasis from a carcinoma of the stomach. Subsequent films showed no change.

of the chest, arm, and upper abdomen of two months' duration. She was known to have had diabetes for five years. A tentative diagnosis of diabetic neuritis was made. A roentgenogram of the chest (figure 6) revealed a dense, rounded, sharply defined shadow at the left base. Since this shadow was regarded as a possible metastatic lesion, although the roentgenologist interpreted it as a Ghon focus, the patient was admitted to the neurological service for further study with a tentative diagnosis of secondary carcinoma of the spine.

Physical examination revealed no changes other than several diffuse neurological abnormalities. Laboratory studies showed nothing remarkable. Roentgen examination of the spine showed osteoarthritic changes in the lower thoracic region.

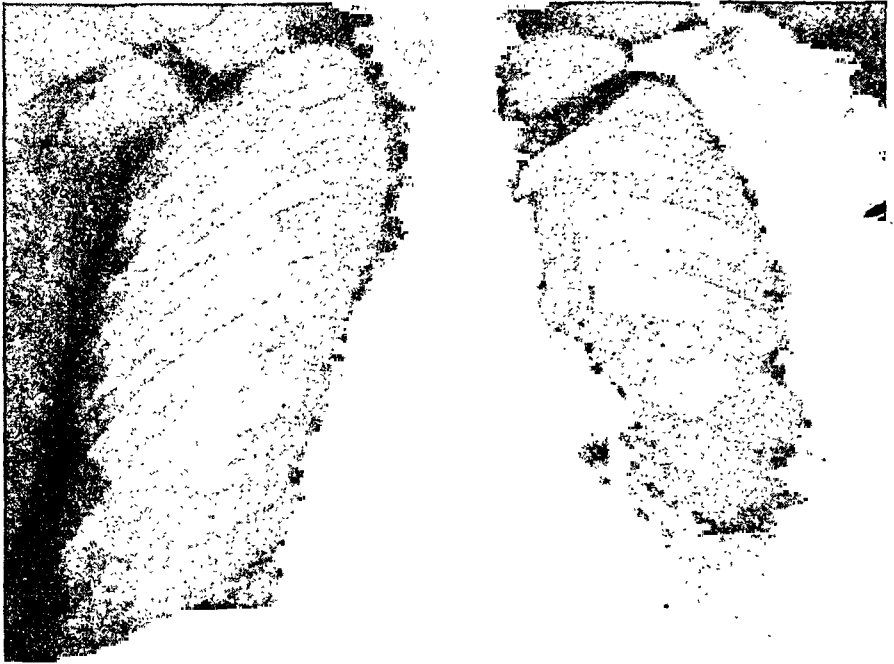


FIG. 6. *Case 4.* Roentgenogram showing shadow in lower left lung field representing a healed tuberculous focus but first considered a metastatic carcinoma. Subsequent films showed no change in size or appearance.

The patient was placed on a diabetic diet and given physical therapy. Her symptoms yielded readily to this treatment. Further roentgenograms of the chest showed no change in the appearance of the shadow, thus indicating that the original impression of metastasis was incorrect and that it was probably a healed tuberculous focus. She was discharged with the diagnosis of radiculitis due to osteoarthritis of the spine.

DISCUSSION

The discovery by roentgenogram of four examples of rather large solitary nodular infiltrations representing healed tuberculous foci within a relatively short period of time indicates that such lesions may not be very rare. Shanks, Kerley and Twining¹⁰ show a picture of a large calcified shadow which did not change in appearance over a period of 14 years. Meyer⁷ shows a photograph of a large tuberculous nodule simulating a metastatic lesion. Wessler and Jaches¹² state that "an early metastatic new growth especially when it is solitary, may closely resemble an incipient tuberculosis or a tuberculous infiltration may simulate a new growth. Error can usually be avoided by the clinical examination which will disclose a

primary growth and also by a later increase in the size and number of metastases."

In our four cases, the extra-pulmonary features contributed to the initial erroneous interpretation. In three of the four cases, the fact that the lesions did not change in size and appearance over a prolonged period of observation served to establish the correct diagnosis. In the fourth case, the life of the patient (case 1) was terminated by an unrelated condition and the correct interpretation was then indicated by the necropsy findings.

The interpretation of the pathological findings warrants some discussion. As described above, the nodule in the lung presented a lamellated appearance both on gross and microscopic examination; calcific deposits were found between some of the layers. These findings are consistent with the description of healed primary tuberculous lesions as given by Pagel and Henke.⁹ Moreover, these authors state that the presence of lung tissue free of atelectasis or inflammation immediately surrounding the nodule points to a healed primary, rather than post-primary, lesion. Areas of ossification, which, when found, are pathognomonic of a healed primary focus were not seen. A careful search of the section on pulmonary affections in Henke and Lubarsch's treatise on Pathology failed to reveal any other condition in which the lesion resembled the one in our case. It seems reasonable to state, therefore, that this nodule was a healed tuberculous, most likely primary, focus. Incidentally, it is one of the largest specimens of this lesion which we have been able to find on record.

Not only must healed tuberculous foci be differentiated from metastatic lesions which are usually asymptomatic but occasionally primary pulmonary neoplasms, either malignant or benign (such as chondroma, fibroma, and lipoma), must be ruled out. In view of the current trend toward operation in these cases, such differentiation is of the utmost importance. In a recent article by Graham and Singer,⁴ three cases were reported in which calcified pulmonary masses were resected on the basis of the diagnosis of tumor. In one of these (case 2) there were no pulmonary symptoms. In at least two of their cases the specimens as shown in photographs resemble our specimen and are highly suggestive of healed tuberculous foci.

Hirsch⁵ has described sharply circumscribed, dense spherical shadows in cases of polycythemia vera. On the basis of a single roentgen examination they were similar to those noted in our cases. However, in polycythemia, the lesions began to fade after they reached a certain density and completely disappeared, the entire cycle usually lasting about three weeks. This evolution as well as the clinical features should serve to differentiate the lesion from a healed tuberculous focus.

SUMMARY

Four cases are described in each of which a fairly large, dense, rounded, sharply circumscribed solitary shadow was noted in a roentgenogram of

the chest. In each case there were additional clinical and roentgen findings to suggest that these lesions were metastatic from a primary carcinoma elsewhere in the body. In one case necropsy showed a large mass, characteristic of healed tuberculosis, probably primary, and no evidence of a malignant lesion. In the other three cases the clinical course failed to bear out the diagnosis of carcinoma. In these cases the pulmonary shadows observed over a considerable period did not change in size or appearance, indicating the correct interpretation of healed tuberculous foci.

Addendum: Since this paper was submitted for publication, we have seen a patient with carcinoma of the sigmoid colon in whom a roentgenogram of the lungs showed two healed tuberculous foci, at first considered metastatic lesions.

In each of two recent papers (HAIGHT, C. and FARRIS, J. M.: Tuberculoma of the lung, *Jr. Thorac. Surg.*, 1939, ix, 108-116; JONES, J. C. and DOLLEY, F. S.: Lobectomy and pneumonectomy in pulmonary tuberculosis, *Jr. Thorac. Surg.*, 1939, viii, 351-370), there are reports of lobectomy for tuberculoma.

We wish to thank Drs. A. A. Epstein, E. D. Friedman, and I. W. Held for permission to report cases from their respective services. We should also like to express our appreciation to Dr. I. Seth Hirsch for aid in interpreting the roentgenograms, to Dr. A. Plaut for his study of the necropsy material in case 1, and to Dr. H. Wessler for valuable criticism.

BIBLIOGRAPHY

1. BIGLER, J. A.: Interpretation of roentgenograms of the chest in children based on observations at necropsy. II. Tuberculosis, *Am. Jr. Dis. Child.*, 1929, xxxviii, 1166-1182.
2. FRIED, B. M.: The primary complex (initial anatomic lesion in childhood type of tuberculosis), a historical study, *Arch. Path.*, 1936, xxii, 829-839.
3. GHON, quoted by SCHICK, B.: Tuberculosis in childhood, *Med. Clin. N. Am.*, 1936, xx, 719-736.
4. GRAHAM, E. A., and SINGER, J. J.: Three cases of resection of calcified pulmonary abscess (or tuberculosis) simulating tumor, *Jr. Thorac. Surg.*, 1936, vi, 173-183.
5. HIRSCH, I. S.: Pulmonary changes in polycythemia vera, *Radiology*, 1936, xxvi, 469-473.
6. KÖHLER, A.: Roentgenology, Transl. from 5th Edition by A. Turnbull, 1928, Wm. Wood, N. Y., p. 315.
7. MEYER, W. H.: Clinical roentgen pathology of thoracic lesions, 1932, Lea & Febiger, Philadelphia, p. 134.
8. MYERS, J. A., HARRINGTON, F. E., STEWART, C. A., and WOLFF, M.: First-infection-type tuberculosis, *Am. Rev. Tuberc.*, 1935, xxxii, 631-643.
9. PAGEL, W., and HENKE, F.: Lungentuberkulose, in Henke-Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, 1930, Springer, Berlin, Vol. III, part 2, p. 190.
10. SHANKS, S. C., KERLEY, P., and TWINING, E. W.: A text-book of x-ray diagnosis, 1938, H. K. Lewis, London, Vol. I, p. 315.
11. WALLGREN, A.: Primary pulmonary tuberculosis in childhood, *Am. Jr. Dis. Child.*, 1935, xlix, 1105-1136.
12. WESSLER, H., and JACHES, L.: Clinical roentgenology of diseases of the chest, 1923, Southworth Publishing Co., Troy, p. 71.

THE HIPPURIC ACID TEST IN HYPERTHYROIDISM *

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F.A.C.P., and MARSCHELLE H. POWER, Ph.D., *Rochester, Minnesota*

FOR many years it has been known that disturbances in the function of the liver might occur in severe exophthalmic goiter. Jaundice has been recognized to be a serious, and usually late, development in the crisis of exophthalmic goiter.

In cases of this type livers have frequently showed changes designated by Robertson¹ as "subacute yellow atrophy." In 1933, Weller² found a patchy, chronic parenchymatous, interlobar hepatitis in many of the livers of patients with exophthalmic goiter. In the same year, Beaver and Pemberton³ studied the livers of 107 patients with exophthalmic goiter and found acute degenerative lesions, simple atrophy, or subacute toxic atrophy and toxic cirrhosis in a high percentage of their cases. They expressed the opinion that these changes were a part of the syndrome of exophthalmic goiter and were related to the severity of the disease. Kuriyama, in 1918,⁴ found that the feeding of thyroid to animals was followed by a rapid loss of glycogen from the liver.

FUNCTIONAL TESTS

Hepatic functional tests have been studied in hyperthyroidism in recent years. Sanger and Hun,⁵ as a result of studies of glucose utilization in hyperthyroidism, concluded that in this disease there is probably a failure of storage of glucose in the liver, due to a toxic change in the liver caused by the disease. In 1926, Youmans and Warfield,⁶ studying the liver function by the phenoltetrachlorophthalein test as well as other tests, found impairment of liver function indicated by the tests in 50 per cent of their 44 cases. They found a relation between the impairment of liver function and loss of weight. Bartels,⁷ using the hippuric acid test of Quick,⁸ studied 148 cases of hyperthyroidism, and found a normal response to this test in only 18 cases. He concluded that the results of the test indicate a degree of change in liver function in direct relation to the severity of hyperthyroidism, but found absence of weight loss or a history of previous iodine medication in patients with a normal liver function as measured by the test on admission. The liver function improved after preoperative treatment in exophthalmic goiter cases, and was usually normal three months after thyroidectomy. A high carbohydrate diet apparently caused improvement in some cases. Recently Quick⁹ has described a method for doing the hippuric acid test by the intravenous injection of 1.77 gm. of sodium benzoate and the determination of hippuric acid excretion in the urine in the hour following the injection.

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PRESENT STUDY

In an attempt to determine whether or not the hippuric acid test would be of value in the handling of patients with hyperthyroidism, and whether or not it could give any information regarding the pathologic physiology of this condition, the test has been carried out in 17 cases of adenomatous goiter with hyperthyroidism and 61 cases of exophthalmic goiter. In the first group, nine of the 17 cases were tested by the oral method, and in the latter group, 42 cases were tested by the oral method. In the other cases, the intravenous test was used. In the few cases in which both methods of testing were used, comparable results were obtained by the two methods. In doing the test by the oral method the urine was collected for four hours after the oral administration of 6.0 gm. of sodium benzoate. In doing the test by the intravenous method 1.77 gm. of sodium benzoate were injected intravenously and the urine was collected for one hour after that. The hippuric acid in the urine was determined in either case by the method of Griffith.¹⁰ Normal results stated by Quick are, for the oral method, 3.0 gm. of benzoic acid (equivalent to 4.41 gm. of hippuric acid) and, for the intravenous method, 0.7 to 0.95 gm. of benzoic acid (equivalent to 1.0 to 1.4 gm. of hippuric acid). Tests done on patients with cardiac decompensation or known urea retention are not included in this study.

CORRELATION WITH BROMSULFALEIN TEST

Snell and Plunkett,¹¹ using the hippuric acid test (oral) in patients with liver disease and comparing it with other tests of hepatic function, found that the synthesis of hippuric acid is a reasonably accurate and satisfactory test for the determination of parenchymatous hepatic damage. They concluded that the excretion of 1.5 gm. or less of hippuric acid is probably indicative of severe damage to the hepatic parenchyma. We have done both the bromsulfalein test and the hippuric acid test either orally or intravenously in 22 cases of hyperthyroidism, 19 of them cases of exophthalmic goiter. An attempt was made to do the tests as closely together as possible; in the majority of instances they were done on consecutive days. The results are noted in table 1. It is to be noted that very low hippuric acid output may occur in the absence of dye retention, but that in all cases with dye retention greater than grade 1, on the basis of 1 to 4, there was some reduction of hippuric acid output. This would add to Quick's and Snell and Plunkett's evidence that hepatic lesions have an influence on the rate of synthesis of hippuric acid in human beings.

CORRELATION WITH BASAL METABOLIC RATE

There is no constant and accurate criterion of the severity of hyperthyroidism; however, in a large group of cases the height of the basal metabolic rate will correlate reasonably accurately with the severity of the disease, and as this is our most accurate estimate that can be expressed

TABLE I
Comparison of Bromsulfalein Test and Hippuric Acid Test

	Bromsulfalein retention, grade *	Hippuric acid, gm. (oral)	Hippuric acid, gm. (intraven.)
Exophthalmic goiter	0	1.1	
	0	2.9	
	0	3.0	
	0	3.1	
	0	3.3	
	0	3.4	
	0	3.7	
	0	4.2	
	0		0.7
	0		0.3
	1	2.5	
	1	4.4	
	1	5.0	
	2	1.9	
	2	2.8	
	3		0.4
Adenomatous goiter with hyper- thyroidism	4	0.5	
	4	1.4	0.5
	4	1.7	
Low basal metabolic rate	0		0.3
	0	3.8	
	1	2.8	0.6
Low basal metabolic rate	1	4.5	

* On a basis of 1 to 4.

numerically, the outputs of hippuric acid have been compared with the basal metabolic rates. The results are best expressed in figure 1. The average hippuric acid output with the oral test in patients with basal metabolic rates of less than + 40 per cent is 3.42 gm. while in those with basal metabolic rates of + 40 per cent or greater it is 2.85 gm. of hippuric acid. When the test was done by the intravenous method the average was 0.98 gm. in the first group and 0.95 gm. in the second. It is to be noted that many patients with only slight elevations of the basal metabolic rate had reduced outputs of hippuric acid. These were not in all cases patients who had been seriously ill before coming to The Mayo Clinic. In some instances very low outputs of hippuric acid were encountered in young patients with exophthalmic goiter of moderate intensity and very short duration. However, there is, in general, a slight negative correlation between the severity of hyperthyroidism and the output of hippuric acid. This fact was first noted by Bartels.

We question the significance of hippuric acid outputs of 3 gm. or more when the oral test is done. Only 16 out of 41 patients with exophthalmic goiter had hippuric acid outputs less than this figure.

WEIGHT LOSS AND DURATION OF HYPERTHYROIDISM.

In our cases we found no correlation between loss of weight and hippuric acid excretion. In one instance in which no weight had been lost the oral

intake was followed by excretion of only 0.9 gm. of hippuric acid. Weight losses of 52 and 60 pounds were noted in patients with normal hippuric acid outputs.

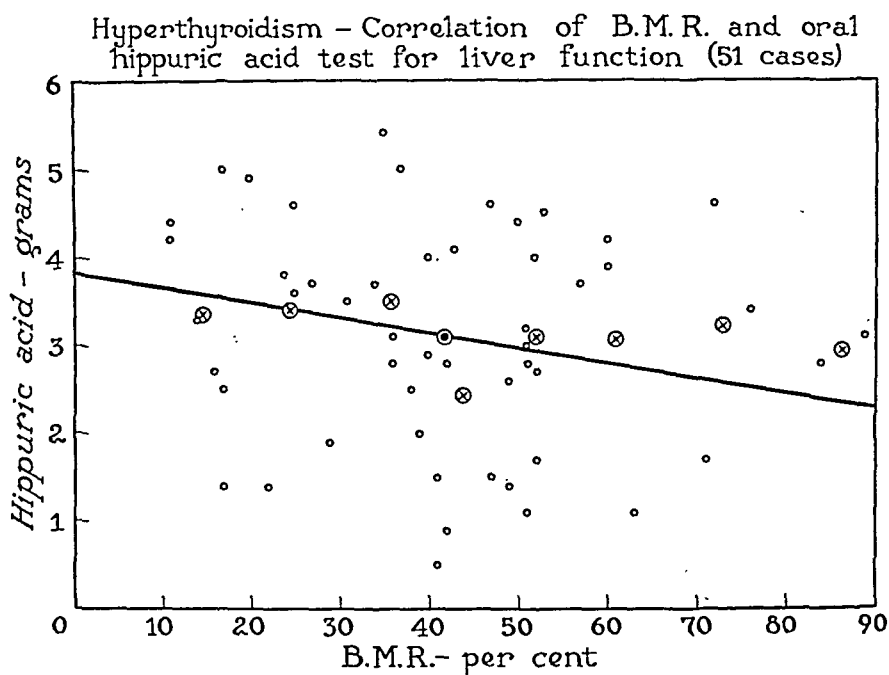


FIG. 1. Correlation of basal metabolic rate and the results of the oral hippuric acid test.

Our findings agreed with Bartels' in finding no correlation between hippuric acid excretion and the duration of hyperthyroidism. The average hippuric acid excretion in cases of exophthalmic goiter of a duration of one year or less is 3.13 gm. whereas in those with a duration of more than one year it was 3.05 gm. No statistically significant variation could be found in this regard. Inasmuch as the duration of hyperthyroidism is so important in relation to surgical risk of thyroidectomy, it would seem that this test does not indicate the deciding factor in this regard.

VITAMINS

Recent work indicating vitamin deficiency¹² in hyperthyroidism and showing regeneration in the liver glycogen and gain in weight in hyperthyroid animals given B₁ and B complex¹³ suggested the desirability of investigating the possible effect of these vitamins on the hippuric acid excretion. It was necessary to limit the time of administration of the vitamins used to the usual period of preoperative preparation, and it was necessary to give all the patients Lugol's solution during that time. Those patients to whom vitamin B was given received 9.9 mg. of thiamin chloride daily except one patient who received 200 mg. of thiamin chloride intravenously in a period of six days. There was a tendency toward increase in the hippuric acid excretion in most cases during the period of treatment. This improvement corre-

sponded closely to the improvement noted with Lugol's solution alone. Two patients, both severely hyperthyroid for many years, and both having markedly reduced hippuric acid excretion, were given thiamin and brewers' yeast over periods of four and six weeks without change in the hippuric acid excretion in one case, and in the other, with only slight improvement of the degree frequently seen after administration of iodine. The possible effect on hippuric acid excretion of vitamins given over longer periods of time should be determined.

GLYCINE

Quick reported an increase in the output of hippuric acid when glycine is given to the patient. In an attempt to determine whether the reduced excretion found in these patients was due to a lack of available glycine or failure of conjugation of glycine and benzoic acid, eight patients were given glycine in doses of 4 to 8 gm. three times a day for two to three days, and, immediately after a single dose of 8 gm., the test was repeated. The results were not consistent, and further study will have to be made to determine the reason for this. The results of glycine administration are shown in table 2.

TABLE II
The Effect of Glycine on the Hippuric Acid Test

B.M.R. %	Weight loss (lbs.)	Hippuric acid, gm.		Method	Dye test (retention, grade*)
		Before glycine	After glycine		
+47	47	1.5	1.4	Oral	
+49	49	2.6	3.1	Oral	
+36	25	2.8	5.4	Oral	
+39	31	2.0	5.2	Oral	
+51	27	3.2	3.5	Oral	
+78	60	0.3	0.7	Intravenous	
+60		0.7	0.5	Intravenous	3
+91		0.3	1.0	Intravenous	0

* On a basis of 1 to 4.

The reason for the failure of an increase in the hippuric acid output after the administration of glycine in two cases, and the slight increase in two others, is of interest. Whether this phenomenon is due to failure of absorption of glycine, lack of ability to conjugate glycine and benzoic acid, or rapid metabolism of the administered glycine cannot be said at present.

The continuance of the use of glycine in some of these cases, as well as some others not reported here, did not result in any determinable clinical improvement.

COMMENT

The reduction of hippuric acid excretion occurs in a significant number of patients with hyperthyroidism. There is some correlation between the

hippuric acid output and the results of the bromsulfalein liver function test, corroborating the opinions of other investigators that hippuric acid formation is related to liver function. Although there are wide variations, there is some correlation of the results of this test with the basal metabolic rate, the tendency being toward a lower hippuric acid output as the basal metabolic rate rises. No significant correlation could be found between the hippuric acid test and loss of weight, duration of hyperthyroidism, or the administration of vitamin B₁. Preoperative treatment with iodine and whatever supplementary treatment seemed indicated resulted in slight improvement in the test in most cases.

Marked reductions in hippuric acid excretion were found in a few cases of the type long designated by H. S. Plummer¹⁴ as having vital organ degeneration. Pigmentation of the skin is usually a feature of these cases. Ordinarily the surgical risk in such cases is high, and prolonged periods of preoperative treatment are advisable in order to allow opportunities for recovery from visceral damage. The occurrence of significantly low tests in such cases might suggest that the test could be helpful in classifying some cases as needing prolonged preoperative treatment. However, we have found as low tests in young patients with exophthalmic goiter of short duration in whom the usual period of preparation was followed by no unusual reaction. A rising hippuric acid excretion has, in two such cases, been concomitant with a general clinical improvement of the type which, by our usual criteria, has indicated to us that the patient was reaching a status in which operation could be performed relatively safely. In both cases thyroidectomy was done without incident and was followed by no unusual reaction.

In one patient a marked reduction in hippuric acid excretion remained constant throughout a prolonged period of preoperative treatment. A severe reaction characterized by gradually rising temperature and pulse and marked prostration resulted in death 48 hours after operation. The reaction was that usually seen in patients who have had hyperthyroidism for many years. Marked hepatic damage was found at autopsy.

However, we have been unable to show any consistent correlation between hippuric acid excretion and any status which is judged serious on the basis of our present criteria. We do not feel, therefore, that the test can be given a position of importance in the handling of patients with hyperthyroidism. The clinical judgment of visceral damage and of high surgical risk is, as a matter of fact, reasonably accurate, and the criteria for establishment of this judgment are reasonably clear. The test continues to be of interest to us, however, because of its implications regarding the pathologic physiology of the liver in hyperthyroidism, and from this angle further study is desirable. Boyce¹⁵ has cautioned that the "test should not be assumed to tell more than it is supposed to tell," stating that it only interprets liver damage in terms of liver function. It seems probable that marked alterations in this test can occur because of functional changes in the liver that must be of short

duration, and temporary. It is important to remember that our conclusions have only to do with the use of this test in hyperthyroidism in the absence of jaundice and that no suggestions are made here regarding the value of the test in obstructive jaundice.

CONCLUSIONS

The excretion of hippuric acid in Quick's test is reduced in a significant number of cases of hyperthyroidism. This is in agreement with the opinion held in recent years that the liver is frequently functionally disturbed in hyperthyroidism.

Reduction of the excretion of hippuric acid is correlated inversely to a slight degree with the basal metabolic rate.

Excretion of hippuric acid is usually diminished when the bromsulfalein test shows retention of dye and is also decreased in some other cases.

The excretion of hippuric acid is not uniformly reduced in patients, who, by other criteria, may be assumed to have a high surgical risk, nor do all patients with marked reduction in excretion of hippuric acid present other criteria suggesting high surgical risk. This study would not indicate, therefore, that the test is of great value in management of hyperthyroidism. The test cannot replace any factor of clinical judgment in regard to hyperthyroidism.

Further study of the physiologic implications of this test in hyperthyroidism should be carried out.

REFERENCES

1. ROBERTSON, H. E.: Personal communication to the authors.
2. WELLER, C. V.: Hepatic pathology in exophthalmic goiter, *ANN. INT. MED.*, 1933, vii, 543-560.
3. BEAVER, D. C., and PEMBERTON, J. DEJ.: The pathologic anatomy of the liver in exophthalmic goiter, *ANN. INT. MED.*, 1933, vii, 687-708.
4. KURIYAMA, SHIGENBOU: The influence of thyroid feeding upon carbohydrate metabolism: I. The storage and mobilization of the liver glycogen in thyroid-fed animals, *Jr. Biol. Chem.*, 1918, xxxiii, 193-205.
5. SANGER, B. J., and HUN, ELSIE G.: The glucose mobilization rate in hyperthyroidism, *Arch. Int. Med.*, 1922, xxx, 397-406.
6. YOUMANS, J. B., and WARFIELD, L. M.: Liver injury in thyrotoxicosis evidenced by decreased functional efficiency, *Arch. Int. Med.*, 1926, xxxvii, 1-17.
7. BARTELS, E. C.: Liver function in hyperthyroidism as determined by the hippuric acid test, *ANN. INT. MED.*, 1938, xii, 652-674.
8. QUICK, A. J.: The synthesis of hippuric acid; a new test of liver function, *Am. Jr. Med. Sci.*, 1933, clxxxv, 630-635.
9. QUICK, A. J.: Personal communication to the authors.
10. GRIFFITH, W. H.: Benzoylated amino acids in the animal organism. III. A method for the determination of hippuric acid and a study of the synthesis of hippuric acid in rabbits, *Jr. Biol. Chem.*, 1926, lxix, 197-208.

11. SNELL, A. M., and PLUNKETT, J. E.: The hippuric acid test for hepatic function; its relation to other tests in general use, *Am. Jr. Digest. Dis. and Nutr.*, 1936, ii, 716-721.
12. WEGELIN, C.: On the antagonism between thyroxine and vitamin A, *West Jr. Surg., Obst. and Gynec.*, 1939, xlvii, 147-154.
13. HIMWICH, H. E., GOLDFARB, WALTER and COWGILL, G. R.: Studies in the physiology of vitamins. XVII. The effect of thyroid administration upon the anorexia characteristic of lack of undifferentiated vitamin B, *Am. Jr. Physiol.*, 1932, xcix, 689-695.
14. PLUMMER, H. S.: The clinical and pathological relationship of simple and exophthalmic goiter, *Am. Jr. Med. Sci.*, 1913, cxlvi, 790-795.
15. BOYCE, F. F.: Hepatic and biliary tract disease; a review of recent significant advances, *Ann. Surg.*, 1939, cix, 351-372.

PSYCHOSIS IN HYPOPARATHYROIDISM; WITH A REPORT OF FIVE CASES *

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PSYCHOSIS is not mentioned as a complication of parathyroid tetany in the usual texts of medicine and in the systems of medicine it is briefly referred to as being very rare. It has been known since 1852 that psychosis may occur in tetany and the subject was reviewed in 1907 by Frankl-Hochwart¹ and in 1920 by Barrett.² In a recent report Barr, MacBryde and Sanders³ mention that psychosis may occur in parathyroid tetany, but they do not state the frequency. It is practically impossible to ascertain the incidence of parathyroid deficiency in the cases of psychosis and tetany described in the older literature. The fact that we have been able to find only four cases reported in the literature⁴ during the past 19 years supports the idea that this complication is very rare. On the other hand, five of the 18 patients with hypoparathyroidism observed at the University Hospital during the past nine years have developed a psychosis. Such a high incidence in this Clinic suggests that the complication occurs more frequently than is generally appreciated.

It appears, therefore, that the occurrence of this complication should be emphasized, that additional cases should be reported, and that certain of the clinical aspects should be discussed.

CASE REPORTS

Case 1. L. F., a white married woman, 34 years of age, entered the University Hospital, March 10, 1922, because of hyperthyroidism. She recovered following a partial thyroidectomy without complications and was sent home 10 days later. She returned November 11, 1929, for a recurrent hyperthyroidism and developed tetany on the fifth day after a subtotal thyroidectomy. The manifestations were partially controlled with calcium lactate orally and she went home to continue this therapy. The symptoms of tetany soon increased and she returned to the hospital April 2, 1930. She was found to have chronic tetany but there were no obvious mental disturbances. She stated, however, that her sexual desires had increased beyond her control and her husband later stated that she had "acted queerly" since her operation. During the sixth day in the hospital she became irritable, exhilarated, talkative, and erotic. Delusions and hallucinations developed and a few hours later she became drowsy and semicomatose. The periods of excitation alternated with those of drowsiness and each usually persisted for several hours. The serum calcium returned to normal 8 days after parathyroid extract and calcium therapy were begun, but the psychosis was unaltered until two weeks later when it began to subside gradually and did not entirely disappear until one month later. She was sent home to continue the above therapy, but it was soon discontinued. Tetany persisted for five years before she developed cataracts which caused her to return to the hospital in August 1936. The serum

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calcium was 4.6 mg. per cent at this time, but there were no mental abnormalities nor had there been any since the previous admission.

Case 2. A single white woman, 35 years of age, entered the University Hospital in September 1929, because of a large, nontoxic nodular goiter. Tetany did not develop following a partial thyroidectomy 13 years previously, but it appeared four days after the subtotal thyroidectomy in 1929. The manifestations were partially controlled with calcium salts and parathyroid extract. She returned home on calcium therapy alone. The symptoms reappeared, however, and she reentered the hospital December 17, 1929, in a confused mental state. She refused to talk and she was hyperactive. Delusions and hallucinations developed during the next six days and the periods of hyperactivity alternated with those of drowsiness in which she was semi-comatosed. The psychosis steadily progressed until five days after the serum calcium had been brought to normal with parathyroid extract and calcium salts. There was then a gradual improvement requiring approximately one month for complete recovery. Continuation of the above treatment was recommended at the time of her discharge, but she did not consistently follow this advice and returned to the hospital several times in chronic tetany until 1938. There had been no recurrence of the psychosis during the interval of eight years of chronic tetany.

Case 3. A white married woman, 44 years of age, entered the University Hospital March 8, 1933, because of hyperthyroidism. Parathyroid tetany developed 10 days after subtotal thyroidectomy. Mental confusion, hallucinations, extreme anxiety, and delusions of persecution appeared during the following six days and suicide was attempted. The psychosis continued until 13 days after the serum calcium had been brought to normal with calcium salts and parathyroid extract therapy. There was then a gradual improvement for three weeks but at this time confusion and delusions reappeared and suicide was again attempted. Hyperactivity became so extreme that it became necessary to restrain the patient for several days. Improvement was rapid for the next five days and she was able to return home although the psychosis had not subsided entirely.

Case 4. A white, married man, 45 years of age, entered the University Hospital, May 16, 1934, for parathyroid tetany. The tetany had appeared four days after a subtotal thyroidectomy five months previously. The symptoms had been controlled with parathyroid extract, but he had objected to the hypodermic injections and had omitted them. Chronic tetany was found to be present and the serum calcium was 6.8 mg. per cent. The second day in the hospital before treatment was instituted he became restless, refused to eat or drink, began to moan and groan, developed fecal and urinary incontinence, became excited, and developed sexual hallucinations. Convulsions and carpopedal spasm were conspicuous by their absence. Parathyroid extract and calcium therapy were then begun, and eight days later the serum calcium had reached normal. The psychosis, however, increased during this time and continued unaltered for another eight days. This was followed by a gradual improvement which required 30 days before the mental status was regarded as normal. He returned home with instructions to continue the above therapy, but did not follow the advice and was readmitted to the hospital six months later in chronic tetany. He denied having had any mental disturbances since his last visit and there were no evidences of psychosis at the time of this examination.

Case 5. A white widow, 63 years of age, entered the University Hospital, April 24, 1938, because of recurrent hyperthyroidism. On the fifth day following the subtotal thyroidectomy she became depressed, refused to eat, and developed delusions. During the next nine days she became delirious and attempted suicide. Another 10 days elapsed without alteration in the mental symptoms when she began to have convulsions. At this time the presence of parathyroid tetany was recognized. The convulsions ceased two days after institution of calcium and dihydrotachysterol therapy although another 14 days passed before the serum calcium had risen to normal.

During this time the psychosis improved remarkably, but three days later convulsions reappeared and the psychosis became aggravated to its previous intensity. The serum calcium was found to be 13.0 mg. per cent. The above therapy was then discontinued and convulsions ceased two days later. The psychosis, however, persisted for another five days and subsided gradually, requiring 35 days to completely disappear.

COMMENT

The usual type of psychosis which accompanies parathyroid tetany is a toxic delirium, although other types including actual dementia have been described. It is generally agreed that there is no specific type of psychosis in tetany. The following symptoms: anxiety, depression, and a sense of impending disaster are common, but they are rarely of sufficient intensity to be classified as a psychosis. Our cases are typical examples of a toxic delirium in which delusions and hallucinations developed. Sexual hallucinations were present in two of our cases (1 and 4) and in both instances the sexual drive had been greatly augmented previous to the appearance of the psychosis. Delusions of persecution also occurred in two cases (3 and 5) and suicide was attempted in both instances.

It appears that if a psychosis is going to occur in parathyroid tetany, it will develop during the first three or four months of the disease. It may appear the first few days postoperatively (Cases 3 and 5) or it may not develop for several weeks (Cases 1, 2, and 4). Psychic disturbances may be the first and only manifestation observed and the patient's condition may be misapprehended unless the possibility of parathyroid tetany is considered and search is made for the other manifestations, namely, Chvostek's and Trousseau's signs, and the serum calcium level (Case 3). Carpopedal spasms and convulsions are not necessarily present during the psychosis, in fact, they are usually absent (Cases 1, 2, 3, and 4).

The prognosis in the psychosis is usually good. The psychic manifestations may be present only temporarily during and following a convulsion or they may persist for several months. There is usually a delay in the response of the mental condition of from one to four weeks after the serum calcium reaches normal and then another three or four weeks are required for complete recovery. The mental symptoms persisted for several months after successful treatment of parathyroid tetany in the two cases reported by Knospe^{4c} but both patients had a previous psychosis during the hyperthyroidism and this fact may account for the longer duration of the psychic disturbances in his patients.

A psychosis is not likely to recur if it has definitely subsided even though tetany returns. Cases 1, 2, and 4, of our series were observed for 6 and 8 years and 6 months respectively after the psychosis had subsided, and after return of the tetany without a return of psychic disturbances. Organic cerebral changes occur undoubtedly in cases of dementia associated with tetany, but the importance of tetany as an etiologic factor in the production of such alterations is questionable. It was suggested by Barr, MacBryde and Sanders⁸ that edema of the cerebrum and meninges may be a contributing

factor in producing cerebral and psychic manifestations after they had observed two patients with papilledema and an increase in intrathecal pressure. The calcium content of the cerebrospinal fluid was normal in their cases, whereas the serum calcium was low. Such circumstances were said to be favorable for the production of edema of the brain. Gregory and Andersch⁵ had previously shown that the calcium content of the cerebrospinal fluid did not necessarily coincide with that of the blood serum. The calcium content of the cerebrospinal fluid was not measured in any of our cases, but the intrathecal pressure was normal in three (Cases 2, 4, and 5) when measured several times during the psychosis and several careful ophthalmoscopic examinations during the psychic disturbances in each of our cases revealed no papilledema. Careful neurologic examinations showed no persistent manifestations of organic central nervous system lesions in any of our cases.

The factors which produce the psychosis are not known. The fact that it occurs comparatively early in the tetany and that it does not recur, although the parathyroid deficiency may relapse, suggests that it is due to failure of adjustment of the cerebrum to the acute chemical changes. Such a hypothesis is supported by the great aggravation of the psychic manifestations in Case 5 during the occurrence of hypercalcemia. Against such a theory is the delayed response of the psychic disturbances as compared to the chemical response to adequate therapy.

SUMMARY

Parathyroid tetany is complicated by psychosis more commonly than is generally appreciated. The complication occurred in 5 of 18 cases, and these 5 cases are reported. The psychic disturbances are usually of the toxic delirium type, occurring during the first few months, and may be the only obvious manifestation of tetany. The prognosis is good and it is not likely to recur although the parathyroid deficiency may relapse. The response to adequate treatment is slower than are the other manifestations of tetany and three or four weeks or several months may elapse after adequate control of the tetany before the psychosis subsides.

BIBLIOGRAPHY

1. FRANKL-HOCHWART, L. VON: *Die Tetanie*, 2. Aufl., 1907, Wien and Leipzig.
2. BARRETT, A. M.: Psychosis associated with tetany, *Am. Jr. Insanity*, 1919-1920, lxxvi, 373-392.
3. BARR, D. P., MACBRYDE, C. M., and SANDERS, T. E.: Tetany with increased intracranial pressure and papilledema—results from treatment with dihydrotachysterol, *Trans. Assoc. Am. Phys.*, 1938, liii, 227-232.
4. (a) POPEA, A., and DEMETRESCO, T. R.: Tetany and psychosis in nursing mother, *Bruxelles med.*, 1930, x, 708-710.
 (b) POPEA, A., and DEMETRESCO, T. R.: Tetany and psychosis, *Rev. stiint. med.*, 1930, xix, 531-535.
 (c) KNOSPE, H.: Tetany psychoses, *Monatschr. f. Psychiat. u. Neurol.*, 1938, xcix, 503-520.
5. GREGORY, R., and ANDERSCH, M.: The filterable calcium of blood serum, *Am. Jr. Med. Sci.*, 1936, cxcii, 263-271.

CARDIAC ADAPTATIONS IN ACUTE PROGRESSIVE ANOXIA *

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CIRCULATORY REACTIONS IN MAN

THE reactions of the cardiovascular system in man to progressively diminishing oxygen have been repeatedly described, among others by Whitney,¹ Schneider,² Schneider and Truesdell,³ Gellhorn,⁴ and Armstrong.⁶ While there are variations assignable to individual sensitivity, speed in development of anoxia, etc., the following reactions commonly occur in standard rebreathing tests: The heart rate increases, systolic pressure rises slightly and diastolic pressure either remains stationary or changes slightly in upward or downward directions. A dynamic analysis of such data indicates that the diminishing oxygen-carrying capacity of the blood is compensated by increased circulating volume as well as by the greater pulmonary ventilation.

However, initial studies of the human circulation by methods applicable to man yielded but little evidence that the circulating volume increases during anoxia. Thus Schneider and Truesdell³ reported that capillary flow seems to be retarded, that venous pressure falls and that the volume of blood flow through the hand decreases. Subsequent investigators⁷ reported somewhat variable results. Estimations of cardiac output by gasometric methods⁸ either gave no indications of significant changes or indicated a slight tendency toward a decrease. It now appears that the early applications of gasometric methods were not reliable and that the difficulty of using them during anoxic states had not been mastered. Now, authorities^{5, 9} seem to be in agreement that an increase in cardiac minute output plays an important rôle in anoxia and in acclimatization to high altitudes.

ANALYSIS OF REACTIONS IN DOGS

The manner in which such compensatory increase in cardiac minute output occurs cannot be satisfactorily analyzed by studies limited to man. Fortunately, as Sands and De Graff¹⁰ first showed, the cardiovascular reactions during progressive anoxia are essentially the same in dogs, lightly anesthetized by non-volatile anesthetics. It is, therefore, logical to transfer to man other discoveries which could only be made by procedures involving operative technic and the use of refined cardiodynamic apparatus applicable only to animals.

What I shall review consists essentially of some contributions from our own laboratory, reinterpreted, in some instances, in the light of other discoveries which have given them new or added practical significance.

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When a lightly anesthetized dog rebreathes air from which oxygen is being continually removed by the body and CO_2 by soda lime, the content of oxygen in the respired mixture decreases evenly from 20 to 5 per cent. The rapidity of the decrease depends upon the size of the respirator used. Figure 1 shows such effects during the course of 90 minutes.

HYPOXIA AND ANOXIA

In interpreting the cardiovascular reactions in such tests it is important to orient ourselves regarding the degree of oxygen deficiency which exists during successive intervals of rebreathing and to determine clearly the stage at which significant oxygen-lack manifests itself. A regularly decreasing percentage of oxygen in the inspired air, as indicated by line O, is not equivalent to an even rate of theoretical ascent to higher altitudes (line A) nor to an even progression of the oxygen deficiency indicated by the calculated oxygen saturation of arterial blood (line HbO). Thus, as shown in figure 1, the animal at the end of the first 40 minutes is at a theoretical elevation of 11,000 ft. and the oxygen saturation of arterial blood has decreased approximately from 20 to 17.8 volumes per cent. During the next 20 minutes partial pressure of oxygen corresponds to an altitude of 19,000 ft. and the blood saturation decreases as much again, i.e., to about 14.5 volume per cent. It is somewhere during this stage—the exact point varying somewhat in different animals—that a significant state of anoxia first exists when an animal is at rest. Beyond this time the blood oxygen decreases more and more rapidly so that after the next 20 minutes it has a value of only 9 volumes per cent and the effects of anoxia become critical for the heart and circulation.

From the viewpoint of cardiac physiology, as established by animal experiments, we may divide the effects of diminishing oxygen lack into two phases, conveniently distinguished by the terms hypoxia and anoxia. In figure 1, the line is arbitrarily drawn at the end of 50 minutes, when the percentage of oxygen rebreathed has been reduced to about 12 per cent, corresponding approximately to the altitude of Pike's Peak. I believe this corresponds roughly, also, to a degree of oxygen deficiency tolerated temporarily, without significant symptoms, by the majority of humans, provided they remain at rest. It must be remembered, however, that any muscular activity, at any elevation, adds significantly to the degree of oxygen deficiency, due to reduced oxygen pressure alone.

CARDIOVASCULAR REACTIONS DURING HYPOXIA

By recording carotid pressures by means of calibrated optical manometers, Sands and De Graff¹⁰ showed that significant changes occur during the stage of hypoxia. As indicated graphically in figure 1, the heart accelerates considerably, systolic pressure rises significantly, and usually diastolic pressure as well. Concurrently, *effective venous pressure* tends to decrease somewhat. In short, the cardiac and circulatory changes must be considered anticipatory

to the time when serious oxygen deficiency occurs, and generally precede compensatory respiratory changes which do not become significant until true anoxia begins to develop.

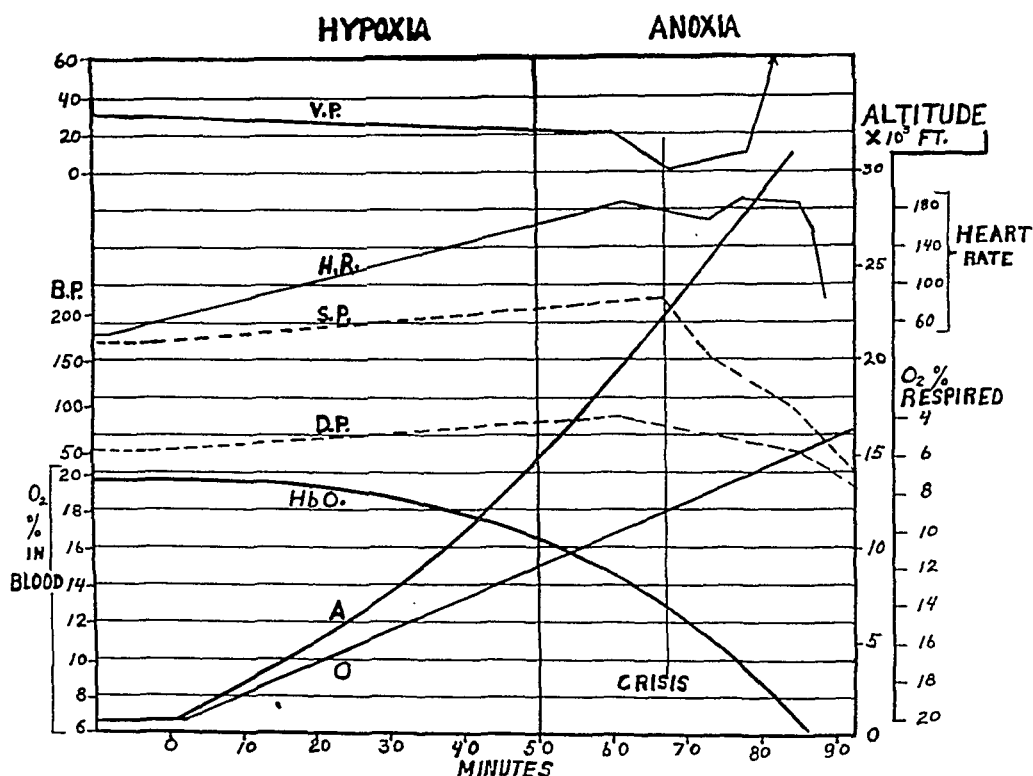


FIG. 1. Graph showing relation of percentage oxygen respired (O) to altitude (A) and oxygen saturation of blood (HbO) and division into stages of hypoxia and anoxia. Smoothed curves showing trend of reactions of heart rate (H.R.), venous (V.P.), systolic (S.P.) and diastolic (D.P.) pressures in dogs during progressive hypoxia and anoxia.

The cardiac acceleration, which is much greater than in similar rebreathing tests in man, is the dominant reaction during the stage of hypoxia. It is due chiefly to progressive reduction in vagal tone, for acceleration is slight if the animals have been previously vagotomized. The fact that some increase in heart rate still occurs, together with the marked decrease in the systole/cycle ratio in normal animals, strongly suggests that sympathetic stimulation or some other adrenergic action is also involved (Sands and De Graff¹⁰).

When changes in cardiac output are recorded in "open-chest" dogs by placing a cardiometer around the ventricles, the changes that occur during progressive rebreathing are not always consistent. The stroke volume decreases; but the calculated minute output may show either an increase or a decrease. We shall discuss this matter later. Oncometer studies have shown that the limbs and kidneys generally increase in size, while the spleen volume diminishes. The blood flow through various portions of the brain

increases. These changes indicate that a redistribution of blood flow occurs, probably due to reciprocal vasomotor actions.

I have made calculations of the total peripheral resistance during hypoxia, using the formula $R = \frac{P_m \times 1332}{V_t} = \frac{\text{dynes} \cdot \text{sec.}}{\text{cm.}^5}$. In this equation, P_m

denotes mean pressure in mm. Hg, V_t , the cardiac output per sec. Such calculations invariably indicate that the total resistance to "run off" from the aorta is decreased during hypoxia. However, recent studies¹² make it questionable whether such deductions are allowable, because they do not evaluate possible active changes in the diameter and elasticity of the aorta. Similarly, the magnitude of vasomotor changes cannot be estimated quantitatively by actual or percentile changes in mean pressure, as is commonly done.

The slight decline of venous pressure has been interpreted as indicative of changes in the peripheral circulation and a reduced venous return to the heart. This has not been demonstrated, and it is equally probable that it is due to the greater minute output of the heart.

CARDIOVASCULAR CHANGES DURING ANOXIA

During the much briefer stage of true anoxia, as defined above, the acceleration of the heart has nearly reached a maximum. Consequently, other compensatory reactions must occur if the minute output is to increase further. The question whether oxygen deficiency at this or earlier stages exerts an initial stimulating action on the ventricles prior to its late depressant action has generally been answered negatively. I have already called attention to my own cardiometer experiments indicating that the stroke volume decreases; *but* whether such decrease is greater or less than would be anticipated in accordance with Y. Henderson's law of cardiac behavior is difficult to determine from such experiments. Most laboratory investigators, among them Mathison,¹³ Doi,¹⁴ Gremels and Starling,¹⁵ Jarisch and Wastl,¹⁶ conclude that oxygen has no stimulating action on the ventricles, but that dilatation and depression result when blood is about half-saturated with oxygen.

With these conclusions, observations in our laboratory do not agree. Sands and De Graff,¹⁰ recorded left ventricular and aortic pressure curves by optical manometers, in vagotomized dogs. In experiments in which heart rate and diastolic aortic pressure did not change, the ventricular pressure curves indicated the uncomplicated responses of the myocardium to decreasing oxygen. A few segments of such records are reproduced in figure 2. During hypoxia, no significant changes are found. As anoxia develops, the ventricular pressure curves (lower records) exhibit a more rapid gradient, and rise to a higher level despite the fact that no measurable increase occurs in the initial tension (at x), just previous to contraction. The aortic pressure pulses (upper curves) have a larger amplitude, which at constant diastolic pressure suggests a greater systolic discharge. The period of ejection,

included between the vertical lines, is reduced. All of these features indicate a stimulating action of anoxia which is not dissimilar to that of minute doses of epinephrine.

In evaluating effects of anoxia on cardiac output by cardiometric registration it is essential that heart rate and arterial diastolic and venous pressure

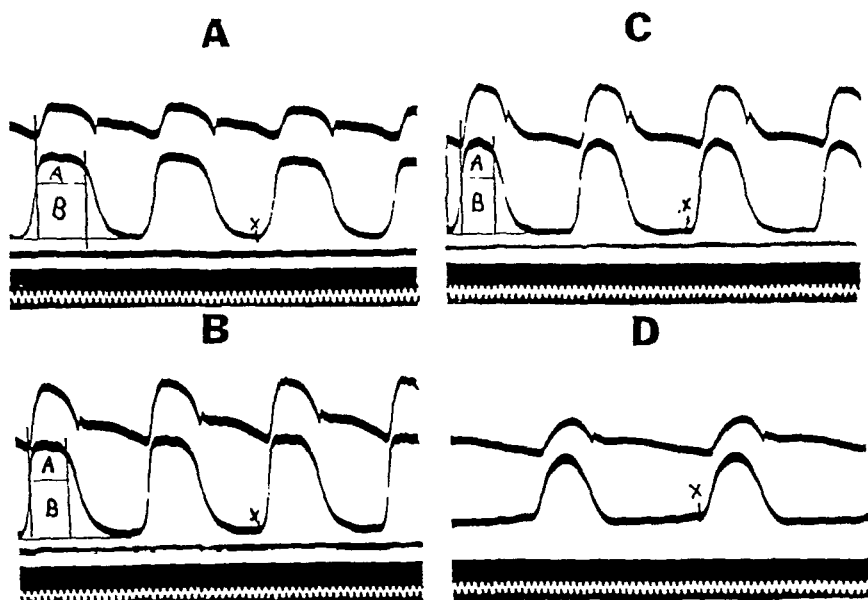


FIG. 2. Four segments of records showing changes in aortic (upper) and ventricular (lower) pressure pulses. A, normal, B at 10 per cent oxygen, C at 8 per cent oxygen, and D at 6.5 per cent oxygen in respired gas mixtures—from controlled circulation experiment. X indicates initial tension; vertical lines, duration of ejection; and ratio of area A to B, economy of effort.

be kept constant, otherwise secondary actions becloud the interpretations (Wiggers and Katz¹⁷). Furthermore, meticulous attention must be given to maintenance of an accurate placement of the cardiometer, which is often difficult to do over long periods, such as are involved in progressive anoxia experiments. I have, therefore, studied the acute effects when dogs were artificially ventilated with gas mixtures containing 6 per cent oxygen in nitrogen. In such tests cardiometer records are apt to be more reliable, for the effects begin within one minute and the whole test is completed in five minutes or less. As illustrated by figure 3, the diastolic size and the stroke volume increase within a minute or two, and continue to do so for several minutes before they are less than normal. Similar effects on cardiac output were reported by Tinsley Harrison and associates¹⁸ and by Gollwitzer-Meier¹⁹ who employed the Fick principle.

The most convincing demonstration that anoxia initially increases systolic discharge were those of Strughold²⁰ who used "controlled circulation" dogs. This investigator made moving pictures of a properly supported and oriented heart during different stages of hypoxia and anoxia. Following each experiment, every frame of the picture film was projected, enlarged, and re-

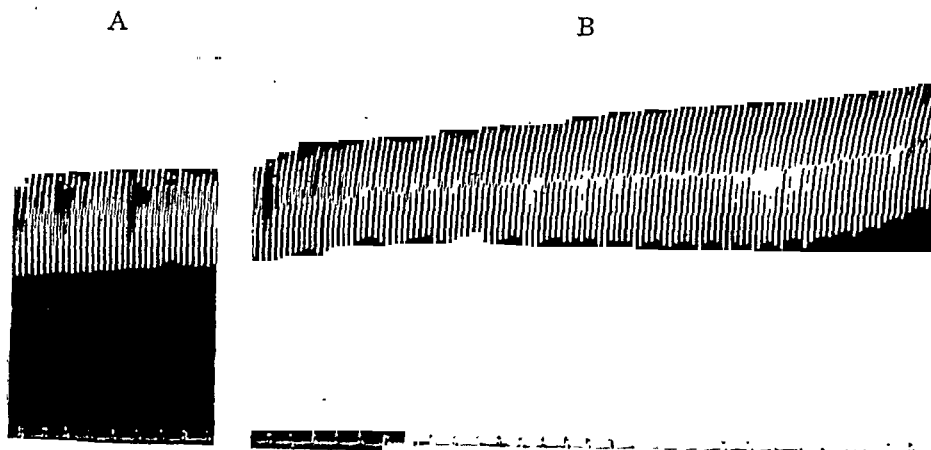


FIG. 3. Volume curves of ventricle, upstroke in diastole (*D*), downstroke during systole (*S*) *D-S* equals stroke volume. *A*, normal control; *B*, 48 sec. after rebreathing 6 per cent oxygen in nitrogen.

drawn, and the surface areas of the ventricles were measured at .03 second intervals. In this way, a plot of systolic ejection and diastolic filling was obtained which resembled a volume curve recorded on rapidly moving paper. During hypoxia no significant changes occurred. However, as shown by the two illustrations of figure 4, a significant increase in diastolic size and

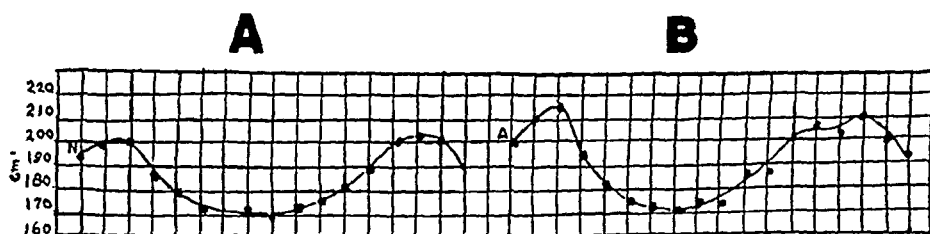


FIG. 4. Volume curves of ventricle, *A*, normal; *B*, after rebreathing 10 per cent oxygen in N (after Strughold).

stroke volume occurred during anoxia (i.e., rebreathing of 10 per cent oxygen.) Since this increase in diastolic size occurred without change in venous pressure, the inference was drawn that perhaps dilation is due to a decrease in myocardial tonus, and that such lengthening of fibers has a beneficial action on the stroke in accordance with Starling's Law.

While the ventricles are thus stimulated, they eject their blood with a greater economy of effort, as judged by a criterion suggested by Katz and myself.²¹ The basis of this criterion may be explained by use of an easily understood comparison: An individual who throws the contents of a pail with some force over a high wall must expend an initial energy in raising the pail above the level of the wall and in holding it at that height, *plus* the energy required to throw its contents over the wall. The first represents *static* and the latter *dynamic energy*. The ratio of the two can be used as an expression of the economy of effort with which the act is executed. Similarly,

the left ventricle expends energy in the static effort of elevating pressure to the aortic diastolic level and of maintaining such a level during ejection. The pressure energy developed over and above this during ejection represents the dynamic effort, for it is immediately utilized to overcome resistance to systolic flow and is converted to kinetic energy of flow during the next diastole. Katz and I²¹ therefore suggested that if, as in figure 2, a ventricular pressure curve is divided into areas *A* and *B*, and these areas are measured, the ratio, area *A*/area *B*, gives an index of the economy of ventricular effort. A glance at the three curves (*A*, *B*, *C*) shows that area *A* becomes somewhat larger with respect to *B* as anoxia increases. Recently, Wright, Hallaran and I²² suggested that the method can be applied to man by recording a reliable subclavian pulse optically and determining the brachial systolic and diastolic pressures at the time. Using this procedure, Ford, Petersilge, Young and I²³ studied the economy of effort index of the human heart during progressive anoxia produced by rebreathing diminishing oxygen volumes. For this purpose, medical students rebreathed CO₂-free air from a segment respirometer of 60 liters capacity. The subject was seated and rested for 30 minutes. After connection with the mouthpiece and while breathing room air in this way, a subclavian pulse was recorded by Frank capsules and brachial pressures were determined. Heart rate could be calculated from records. The subject was then connected to the respirometer in which the percentage of oxygen decreased progressively to 14 per cent in about 5 minutes. At this point, the rebreathing mixture was kept constant by slow admission of oxygen while another set of pulse curves and brachial pressures was recorded. In a similar way, the oxygen was reduced to and stabilized at 12 and 10 per cent respectively; recordings of pulses and blood pressure being again taken. In 20 out of 23 students, in whom reliable records and data for analysis were obtained, a slight increase in efficiency was found when 14 per cent oxygen was rebreathed and a more definite increase while they were rebreathing 12 per cent oxygen. Twelve showed a further increase when the oxygen was reduced to 10 per cent; the other 8 showed some tendency for the index to decrease, but it was still above the initial values. The results indicate that anoxia exerts a stimulating action on the heart in most normal subjects and, aided by lowering of diastolic pressure, the economy with which mechanical energy is utilized is enhanced. The possibility exists that the tendency for the economy of effort to increase or decrease when 10 per cent oxygen is rebreathed may prove valuable as an adjunct to present tests for separating individuals who do and do not tolerate low atmospheric pressures.

This beneficial effect of oxygen deficiency upon the ventricle is replaced by a depressing action as the degree of anoxia becomes extreme. As a rule, this occurs when the decrease in oxygen of the respired air has exceeded 8 or 6 per cent, i.e., corresponding to a reduction of arterial oxygen saturation to 55 or 35 per cent. When this stage is reached a circulatory crisis super-

venes. As shown in the graph of figure 1, arterial pressures fall rapidly, pulse pressure is reduced, the ventricles dilate enormously, systolic discharge decreases and venous pressures rise tremendously. Similar results are reported by Gollwitzer-Meier.¹⁹ As shown in record D of figure 2, despite a great increase in the initial tension (x), the contraction rapidly becomes less vigorous. No evidence exists that failure of the peripheral circulation occurs previous to this time, as claimed by many investigators. *The circulatory crisis is essentially an acute congestive failure of the ventricles due to the extreme anoxia.* Slowing of the heart through central vagal action and many interesting disturbances of conduction and impulse initiation take place. These have been comprehensively analyzed by Greene and Gilbert.²⁴ Dynamically, these disturbances serve to reduce arterial pressures still further.

The consecutive stimulating and depressing effects of anoxia on the myocardium can be demonstrated convincingly in still another manner. Tennant and I,²⁵ by recording the contractions of a small region of the ventricle optically, showed that the area fails to shorten within one minute after the coronary branch to that area is occluded. In such experiments the sequence of hypoxia \rightarrow anoxia occurs within 100 to 125 heart beats. A review of these curves shows a fact which escaped our attention at the time, viz., that during the first 30 to 40 beats following occlusion the myographic contractions are greater. Thereafter, they become smaller and, finally, fail entirely.

THE CORONARY FLOW DURING ANOXIA

When the oxygen in the inspired air is reduced to 8 or 9 per cent, the volume of coronary flow increases tremendously. This was suggested by the increased flow of blood from the coronary sinus noted by Hilton and Eichholtz²⁶ and has recently been proved by H. Green and Wegria²⁷ in this laboratory. These investigators recorded not merely an increase in flow in a coronary ramus but showed by analysis of phasic flow curves that this is due predominantly to dilatation of intramural coronary branches. The pronounced anoxic vasodilation is doubtless a providential mechanism by which the cardiac pump is sustained so well in progressive anoxia; indeed, it is probable that myocardial stimulation is converted into myocardial depression as soon as the augmentation of coronary blood flow cannot keep pace with the decreasing volumes of oxygen carried by the blood.

The thought arises that the great variation in the sensitivity of different individuals to extreme anoxia and their capacity for acclimatization may depend to a large extent upon the compensatory increase in coronary blood flow which is possible. Failure of such compensatory dilatation, due to functional or morphological alterations in the main coronary vessels, may explain the poor cardiac reactions which patients with valvular or myocardial disease experience even at moderate altitudes. It may be anticipated that, when the main coronary branches are sclerotic and narrow, compensatory vasodilation of intramural vessels cannot achieve the same effective improve-

ment of circulation which occurs in the normal heart and that, therefore, such patients assume some risk even in commercial airplane transportation. Autopsy records and experimental studies²⁸ are in accord, however, in demonstrating that, as narrowing of the main vessels gradually takes place, collateral circulations are established from which areas involved may conceivably derive an increased blood flow, during the course of such anoxia. Until more definite evidence is available we should perhaps not be too dogmatic in interdicting air travel to individuals with evident coronary sclerosis.

In concluding this paper, may I add that it is not my purpose to minimize the effects of oxygen deficiency on reflexes and central nervous mechanisms which modulate the action of the heart and control the peripheral vessels. Nor do I suggest that many circulatory reactions of anoxia experienced in man may not involve such nervous actions. It is important, however, that in our zeal to unravel the adjustments of the heart and circulation to anoxia through moderator reflexes and central nervous actions we do not forget the equally important effects which oxygen lack has *directly* on the myocardium and coronary vessels.

SUMMARY

In acute progressive anoxia the supply of oxygen to cells is not solely conditioned by the degree of pulmonary ventilation and the oxygen-carrying capacity of the blood; it involves also an increased blood flow.

The circulatory reactions characteristic for man, breathing gas mixtures with decreasing oxygen volumes ($20 > 6$ per cent) can be duplicated in lightly anesthetized dogs. Such experiments have the advantage that the mechanisms by which cardiac adaptations operate to increase blood flow, can be analyzed more thoroughly than in man.

During hypoxia, corresponding to progressive decrease in respired oxygen volumes to about 12 per cent, to blood oxygen saturations above 75 per cent or altitudes of 15,000 feet, blood flow is increased (*a*) regionally, by reciprocal constriction and dilatation of vessels causing redistribution of blood flow, and (*b*) generally by acceleration of the heart. The latter is due to decreased vagal tone, increased accelerator nerve activity and perhaps some direct effect on the S-A node. Stroke volume is not affected otherwise than during any cardiac acceleration. The vigor of ventricular contractions increases and the period of systolic expulsion shortens. Vasomotor changes probably occur, but there is no dynamic evidence that they are reflected in the changing systolic and diastolic pressures. Effective venous pressures fall slightly, not through reduced venous return but owing to greater minute output by the faster heart.

During true anoxia, which begins when oxygen of the inspired air is progressively decreased below 12 per cent, the heart responds with greater stroke volumes and with further increase in velocity of ejection. The economy of effort is enhanced. Experiments on dogs with "controlled circulation," i.e., in animals whose heart rate, arterial diastolic and venous

pressure, as well as alveolar CO_2 are kept constant, have demonstrated that the increased systolic discharge is accompanied by increase in diastolic size, independently of changes in venous pressure. Such compensatory reactions could probably not occur without the unquestioned dilatation of coronary vessels.

Further decline of oxygen in the inspired air to 7 or 6 per cent, corresponding to arterial oxygen saturations between 50–35 per cent and to altitudes up to 30,000 ft., leads to a circulatory crisis. Arterial pressures decline abruptly, pulse pressure is reduced, systolic discharge decreases, venous pressure rises tremendously, and various types of conduction and rhythm disturbances may occur. No evidence exists that peripheral vasomotor failure is concerned. The circulatory crisis is essentially an acute congestive heart failure due to depressant effect of anoxia on the myocardium. It probably supervenes when the increasing coronary flow can no longer keep pace with the rapidly diminishing tension of oxygen in the blood.

REFERENCES

1. WHITNEY, J. L.: Manual of Med. Research Lab. (Mineola, N. Y.), Gov't Printing Office, Washington, D. C., 1913. Medical studies in aviation. III. Cardiovascular observations, Jr. Am. Med. Assoc., 1918, lxxi, 1389.
2. SCHNEIDER, E. C.: Medical studies in aviation. II. Physiological observations and methods, Jr. Am. Med. Assoc., 1918, lxxi, 1384. Physiological effects of altitude, *Physiol. Rev.*, 1921, i, 631.
3. SCHNEIDER, E. C., and TRUESDELL, D.: The circulatory responses of man to anoxemia, *Am. Jr. Physiol.*, 1924, lxxi, 90.
4. GELLHORN, E.: Circulatory studies on anoxemia in man with respect to posture and CO_2 , *ANN. INT. MED.*, 1937, x, 1267.
GELLHORN, E., and LAMBERT, E. H.: The vasomotor system in anoxia and asphyxia, 1939, University of Illinois Press, Urbana, III.
5. DILL, H. B.: Life, heat and altitude, 1938, p. 186, Harvard University Press, Cambridge, Mass.
6. ARMSTRONG, H. G.: Principles and practice of aviation medicine, 1939, Williams and Wilkins Co., Baltimore.
7. GELLHORN, E., and STECK, I. E.: Effect of inhalation of gases with low O_2 and increased CO_2 tension on peripheral blood flow in man, *Am. Jr. Physiol.*, 1938, cxxiv, 735.
8. DOUGLAS, E. G., HALDANE, J. S., HENDERSON, Y., and SCHNEIDER, E. C.: Physiological observations made on Pike's Peak with special reference to low barometric pressures, *Phil. Trans. Roy. Soc., B*, 1913, cciii, 310.
HASSELBALCH, K. A., and LINDHARD, J.: Zur experimentellen Physiologie des Höhenklimas, *Biochem. Ztschr.*, 1915, lxxviii, 265, 295; 1916, lxxiv, 1.
- BARCROFT, J., BINGER, C. A., BOCK, A. V., et al.: Observations upon the effect of high altitude on the physiological processes of the human body, carried out in the Peruvian Andes, chiefly at Cerro de Pasco, *Phil. Trans. Roy. Soc. London, B*, 1923, ccxi, 351.
- BARCROFT, J.: The respiratory function of the blood. I. Lessons from high altitudes, 1925, Cambridge, England.
9. GROLLMAN, A.: Physiological variations of cardiac output in man (the effect of high altitude), *Am. Jr. Physiol.*, 1930, xciii, 19.
- HERBST, R., and MANIGOLD, K.: Das Verhalten von Kreislauf u. Atmung bei Sauerstoffmangel, *Arbeitsphysiol.*, 1936, ix, 166.

- CHRISTENSEN, E. H., and NIELSEN, H. E.: Die Brauchbarkeit der Fremdgasmethode zur Bestimmung des Minutenvolumens bei niedrigem Druck, *Skand. Arch. Physiol.*, 1936, lxxv, 149.
- CHRISTENSEN, E. H.: Der Kreislauf in grossen Höhen, *Skand. Arch. Physiol.*, 1937, lxxvi, 75.
- MATTHES, K., and MALIKIOSES, X.: Untersuchungen über die Strömungsgeschwindigkeit des Blutes in menschlichen Arterien, *Deutsch. Arch. f. klin. Med.*, 1936, clxxix, 500; *Luftfahrtmedizin*, 1937, i, 259.
10. SANDS, J., and DE GRAFF, A. C.: The effects of progressive anoxemia on the heart and circulation, *Am. Jr. Physiol.*, 1925, lxxiv, 416.
11. SCHMITT, C. F.: The intrinsic regulation of the circulation in the parietal cortex of the cat, *Am. Jr. Physiol.*, 1936, cxiv, 572.
12. DINGLE, J. T., KENT, G. T., WILLIAMS, L. L., and WIGGERS, C. J.: A study of alleged quantitative criteria of vasomotor action, *Am. Jr. Physiol.*, 1940. (In press.)
13. MATHISON, G. C.: Action of asphyxia upon the spinal animal, *Jr. Physiol.*, 1910, xli, 416.
14. DOI, Y.: Studies on respiration and circulation in the cat. I. The influence of an acute anoxic anoxaemia on respiration and circulation, *Jr. Physiol.*, 1921, lv, 43.
15. GREMELS, H., and STARLING, E. H.: On the influence of hydrogen ion concentration and of anoxaemia upon the heart volume, *Jr. Physiol.*, 1936, lxi, 297.
16. JARISCH, A., and WASTL, H.: Observations on the effect of anoxaemia upon heart and circulation, *Jr. Physiol.*, 1926, lxi, 583.
17. WIGGERS, C. J., and KATZ, L. N.: The contour of the ventricular volume curves under different conditions, *Am. Jr. Physiol.*, 1922, lviii, 439.
18. HARRISON, T. R., and BLALOCK, A.: VI. The effects of severe anoxemia of short duration on the cardiac output of morphinized dogs and trained unnarcotized dogs, *Am. Jr. Physiol.*, 1927, lxxx, 169.
- HARRISON, T. R., WILSON, C. P., NEIGHBORS, DE WITT, and PILCHER, C.: VII. The effects of anoxemia of mild degree on the cardiac output of unnarcotized dogs, *Am. Jr. Physiol.*, 1927, lxxxiii, 275.
19. GOLLWITZER-MEIER, KL.: Anoxämie u. Kreislauf, *Pflüger's Arch. f. d. ges. Physiol.*, 1928, ccxx, 434.
20. STRUGHOLD, H.: A cinematographic study of systolic and diastolic heart size with special reference to effects of anoxemia, *Am. Jr. Physiol.*, 1930, xciv, 641.
21. WIGGERS, C. J., and KATZ, L. N.: The static and dynamic effort of the heart during ejection, *Am. Jr. Physiol.*, 1928, lxxxv, 229.
22. WRIGHT, G. W., HALLARAN, W. R., and WIGGERS, C. J.: The economy of effort index from hearts of normal and hypertensive subjects, *Am. Jr. Physiol.*, 1939, cxxvi, 89.
23. FORD, M. L., PETERSILGE, C. L., YOUNG, A. F., and WIGGERS, C. J.: Effect of acute anoxia on the economy of effort index in man, *Proc. Soc. Exper. Biol. and Med.*, 1940, xlv, 353.
24. GREENE, C. W., and GILBERT, N. C.: Studies on the response of the circulation to low oxygen tensions. III, *Arch. Int. Med.*, 1921, xxvii, 517; V, *Am. Jr. Physiol.*, 1921, lvi, 475; VI, 1922, lx, 155.
25. TENNANT, R., and WIGGERS, C. J.: The effect of coronary occlusion on myocardial contraction, *Am. Jr. Physiol.*, 1935, cxii, 351.
26. HILTON, R., and EICHHOLTZ, F.: Chemical factors in coronary circulation, *Jr. Physiol.*, 1925, lix, 413.
27. GREEN, H., and WEGRIA, R. In press (1941).
28. MAUTZ, F. R., and GREGG, D. E.: Dynamics of collateral circulation following chronic occlusion of coronary arteries, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 797.
- GREGG, D. E., THORNTON, J. J., and MAUTZ, F. R.: The magnitude, adequacy and source of the collateral blood flow and pressure in chronically occluded coronary arteries, *Am. Jr. Physiol.*, 1939, cxxvii, 1.

HYSTERIA—SOME COMMON MISCONCEPTIONS *

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GREAT strides have been made in recent years toward dissemination of psychiatric knowledge so that there now exists within the medical profession a generally wholesome attitude toward psychiatric illnesses. This is particularly true of the psychoses. There still exist, however, attitudes on the part of many members of the profession toward certain psychiatric problems which need dispelling. The attitude toward "hysteria" seems to be the worst. It is not at all unusual to see a physician, who has previously displayed an active interest in an illness and the utmost courtesy to the patient suffering therefrom, alter his attitude completely upon receiving a diagnosis of "hysteria" from the consulting neurologist or psychiatrist. The patient usually quite rapidly senses the change and comes to feel that the physician's attitude is one of disgust or pity rather than of interest and sympathy. Therapy under such conditions is doomed to failure.

It is the purpose of this paper to attempt to clarify certain erroneous conceptions regarding "hysteria" which seem to have played a major rôle in fostering these unwholesome attitudes. It is noteworthy that many, perhaps the majority, of practicing physicians include under "hysteria" all the psychoneuroses.

The psychiatric knowledge possessed by the general medical practitioner must of necessity be conditioned by reading psychiatric textbooks rather than by experience. It is, therefore, the textbooks which must be searched first for possible clues to explain these existing misconceptions. It is here that we make our first astounding discovery. The description of "hysteria" and the elaboration of the personality traits of the patient suffering therefrom contained within most of the present-day textbooks are not applicable to the majority of the "hysterical" illnesses or symptoms which are seen by the psychiatrist today. There are reasons for this.

In the past our knowledge of psychiatric illnesses has been achieved for the most part by the study of patients who were delivered in toto to the psychiatrist and usually into the confines of a psychiatric institution, frequently even a state hospital. This is the knowledge recorded in most psychiatric textbooks.

Much of the newer, present-day psychiatric knowledge is being obtained by physicians who practice extramural psychiatry or psychiatry in a general hospital.¹ These physicians are seeing illnesses or oftentimes only isolated symptoms which are obviously "hysterical" or "functional" or "psychologically determined," depending upon which terminology you prefer; yet in very few respects do these illnesses or the patient suffering from them fit

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the concepts of the labeled illnesses of present-day psychiatric textbooks.

In fact, it seems quite likely that following the present intensification of psychiatric education in medical schools wherein a part of the examination of almost every patient studied in the teaching centers is a psychiatric evaluation of his illness, many present-day concepts of psychiatric illnesses will be considerably altered.

There are two very common misconceptions regarding "hysteria" which are closely allied and can be discussed together. First, that "hysterical" symptoms or illnesses are more or less identical with malingering, intimating thereby that the patient is just putting them on. In one book, perhaps unwittingly, the author has listed under "Tests for Malingering" the ways of differentiating "hysterical" from "organic" symptoms and signs.² Second, that no symptom is "hysterical" unless it can be mimicked volitionally.^{6,8}

In discussion it may be pointed out that except in those rare cases of so-called "professional malingering," wherein there is direct monetary gain to be had by faking a non-existent injury, true malingering in psychiatry is for all practical purposes non-existent. Instead of being looked upon as purely volitional, "hysterical" symptoms should be regarded as evidence of illness in the broad sense of the term. The multitude of intricacies entering into the formation of an "hysterical" illness and those various perplexing factors which determine the formation of specific symptoms, whether they be "situational," "physical" or "psychical," are of such complexity that they can rarely ever be either easily or completely understood. The point to be emphasized is that such illnesses should not be denied merely because it is difficult or impossible to completely understand them. Careful and detailed studies by a number of men of various schools of psychiatric thought have scientifically established the illness factor in these cases. It is wise for the physician not thoroughly grounded in psychiatry to just accept this without asking for specific proof in the individual case.

The misconception that nothing is "hysterical" unless it can be mimicked volitionally probably has its roots in the fact that this is often true for the striped muscular phenomena. However, it does not hold true for either the sensory or the visceral manifestations of the illness. It is generally stated concomitantly with the above that the "hysterical" symptom is one which may be reproduced under hypnosis.⁷ This seems to have fixed more strongly in mind the concept that the "hysterical" symptom is, therefore, volitional. In explanation it may be pointed out that there is considerable difference between an individual's ability to perform some act strictly volitionally and his ability to perform the same act while under hypnosis. In addition, almost every psychiatrist has seen "hysterical" symptoms which have not been reproduced under hypnosis.

For the successful treatment of "hysterical" symptoms it sometimes seems wiser to consider them as "organic" nervous system lesions. If the physician assumes this sort of attitude toward the lesion and the patient

suffering therefrom and at the same time is cognizant of the fact that this particular "organic" lesion is the result of disturbances which are mainly "psychologic" and can usually be cured by therapy which is predominantly "psychologic," both the patient and the physician will be much better satisfied with their contacts with each other.

Many physicians feel that the "hysterical" patient is not trying to get over his symptoms or his illness and that if he would only try, he could be well. The blame for this misconception lies on the shoulders of the psychiatrists who have made so popular the misleading terms "flight from reality" and "escape into illness."^{8, 10}

The occasional reader of psychiatry gains the impression when studying the exponents of this misconception that "hysterical" patients quite eagerly and with perfect awareness of what is transpiring avoid unpleasant situations by embarking on this perfectly enjoyable thing called "hysteria." Such is certainly not the case. Patients experiencing an "hysterical" illness, if it is at all severe, almost invariably endure marked suffering at one time or another during the course of the illness. Even those "hysterical" cases who display an outward appearance of indifference to rather disabling symptoms usually suffer considerable discomfort as their symptoms change during the course of therapy.

Instead of looking upon the "hysterical" patient as having "escaped into illness," it is wiser to regard the "hysterical" illness or symptom in one of two ways. Regard it as being the temporary result of an honest effort on the part of the patient to solve a difficult problem. In so trying to solve a difficult problem, the patient's efforts may have been misdirected and the "hysterical" symptoms be the result. But he has really tried to solve the problem. He has not consciously tried to "escape." Another way of looking upon the "hysterical" patient or the "hysterical" symptom is to regard it as being the result of a large number of varied factors (all the way from the constituents of the circulating blood to the excitations set in play by incoming visual stimuli) acting upon the nervous system. Some of these factors may be altered or the intensity of the excitations may be lessened so that a different reaction will ensue. Either of these ways of thinking will stimulate scientific inquiry into the causative factors and point the way toward a more healthy solution or reaction.

The misconception that "hysterical" patients never do anything which results in injury to themselves or else only very minor injury⁷ causes unnecessary accidents. In fact, when a "fit" is suspected of being "hysterical," it is not unusual for the physician to recommend that no attempt be made to catch the patient should he roll from the bed because it is said that the "hysterical" patient will see to it that he is not injured.

This is a good therapeutic practice with some patients but a dangerous one with others and is a decision best left to the specialist. Although there exist cases displaying "hysterical" episodes only when an audience is in attendance, not all "hysterical" episodes are so occasioned.

Despite the laudable effort many physicians are making today to sharply define and separate "epilepsy" and "hysteria,"¹¹ the accomplishment of this in many cases is difficult unless one takes the stand that the diagnosis of "epilepsy" rests upon the demonstration of the characteristic electro-encephalographic cerebral dysrhythmia. It is not fashionable in this day to speak of "hystero-epilepsy," yet the physician should remember that there are cases presenting the syndrome of episodic loss of consciousness with accompanying "fits" but who lack the electro-encephalographic abnormalities seen in "epilepsy" and whose "fits" are often controllable by psychotherapy. They injure themselves or occasionally others in about the same way and about as frequently as "epileptics" do.

There is another group of "hysterical" illnesses, sometimes labeled "dissociation hysteria," in which the patient suffers actual clouding of consciousness with all its attendant dangers and during which he must be protected in the same way that one would protect an acute schizophrenic. While speaking of the injury danger in "hysterical" patients, we should remember that suicide in such cases is not unknown. Attention is called to the statistics on suicide¹² where it is noted that a relatively small percentage of the patients were thought to be psychotic. What then should be the diagnosis pinned to the larger percentage?

Of all the misconceptions regarding "hysteria" the one which most frequently engenders an unwholesome attitude toward the patient and which inclines the physician toward therapeutic nihilism is the belief that every individual suffering from "hysteria" has a specific constitutional inadequacy which predisposes to the development of this particular type of illness.^{4, 9, 13, 14} There is even much written about a specific "hysterical personality." The psychiatric study of all cases coming for medical aid, even for obvious "physical" illnesses, has revealed facts at variance with this misconception.

While it is common knowledge that some individuals react to nearly every unpleasant stimulus with an "hysterical" episode, it is not so generally realized that under the proper conditions, the exact nature of such conditions varying somewhat depending upon the individual in question, any individual—no matter how well born or how well integrated—can be made to display what we today call "hysterical" symptoms. If there is to be described a specific constitutional defect which predisposes to the development of "hysterical" symptoms, then such a description must be used to describe the entire human race and not just a portion thereof.

The difficulty is in deciding what differentiates a few "hysterical" symptoms from "hysteria." A widely read book hints at this when at the start of the chapter on "hysteria" the reader is cautioned against mistaking "hysterics" for "hysteria."⁵ Yet it fails to make clear where one must draw the line. It is to be hoped that some author will attempt a solution of this problem. At the present a generally satisfactory solution does not exist. "Hysteria" today includes within it a numerous and varied set of

related conditions about which the final word has not been written. It is known that there may be all degrees of severity of "hysterical" illnesses just as there may be all degrees of severity of "physical" illnesses.

For proof of the above the following two points are offered to stimulate observation, although innumerable ones could be listed. The psychiatric study of patients who seek medical aid because of obvious "physical" ailments reveals that even many of these patients consistently present signs and symptoms which could not be produced by the isolated pathological lesion but which represent instead the influence of that lesion upon the individual's nervous system (including "psyche") effecting a "functional" or "hysterical" symptom. Such symptoms frequently subside simultaneously with the physician's diagnosis and reassurance of recovery before the pathological lesion has changed one whit.

Those who have had the opportunity to be consulted by medical students have ample proof of this misconception. Medical students are selected from a large group of applicants because of their superior intellectual ability, their excellent hereditary background, their constitutional soundness and a previous record indicating a fine state of integration of their faculties. Yet, at some time during the course of their medical school existence with all its newness, its mysteries, the threats of failure and the excessive demands which such a study-course makes upon one, no small number of these students display either isolated symptoms or else full-blown illnesses which are obviously and frankly "hysterical," usually more politely labeled "functional." Despite suffering these temporary "hysterical" symptoms or illnesses, these same students usually go on to complete recovery and in the future a fine state of mental health as practicing physicians. As well-integrated practicing physicians occupying a respected position in their communities, no one ever looks upon them as having an "hysterical" personality or a specific constitutional defect. Yet these same men have suffered many "hysterical" symptoms.

SUMMARY

It has been pointed out that there still exists within the medical profession a rather unwholesome attitude toward "hysteria" and the patients suffering therefrom. A few of the outstanding misconceptions regarding "hysteria" which tend to promote such an attitude have been discussed. They are in order:

1. That "hysterical" symptoms or illnesses are more or less identical with malingering, intimating thereby that the patient is just putting them on.
2. That no symptom is "hysterical" unless it can be mimicked volitionally.
3. That the "hysterical" patient is not trying to get over his illness and that if he would only try, he could be well.

4. That "hysterical" patients never do anything which results in injury to themselves or else only very minor injury.

5. That patients suffering from "hysteria" have a specific constitutional defect which predisposes to the development of this illness.

A case contradicting almost all of these common misconceptions is presented in brief.

Case Report. J. L., aged 57, was admitted to the hospital with the complaints of blindness, paralysis and pains in the back and legs. Family history showed only that the father and mother lived to advanced ages and that the patient was one of nine farm-raised siblings. Past health had been excellent. The patient had been married 38 years and had six living children. Patient had made a satisfactory living as both farmer and night watchman in a sawmill, and was considered by his friends and family as having been a well-adjusted and stable individual prior to his present illness. The present illness had begun seven years prior to entry with the gradual onset of pains of intermittent nature in his lower extremities. These pains were not severe enough to keep the patient from working. Eighteen months prior to entry patient had the onset of a period of disturbed consciousness lasting about five minutes and followed by markedly diminished vision and dizziness. During the next several weeks spent in bed he developed various tremors of face, hands and legs. After several weeks his vision partially returned and he was able to walk about the house with aid. During the next several months he had repeated attacks, each similar to the first. The last attack occurred six months before admission, since which time he had not been able to distinguish between light and dark. The tremors increased in severity, particularly about the face and upper extremities. For the most part he had been bedfast, at times unable to move his lower limbs at all, due to increasing stiffness.

Physical examination showed a malnourished, middle-aged white man with evidence of marked weight loss and moderate dehydration. There was purulent exudate from the ocular conjunctivae. The eyelids were in a constant state of motion, alternately opening and closing, while the eyeballs also constantly moved slightly in an upward and downward motion but could not be moved to either side. Pupils responded to light but light perception was absent. The disks were quite difficult to visualize; they appeared somewhat pale but well outlined. There was marked dental caries, and the tongue was dry and coated. There was moderate generalized arteriosclerosis with normal blood pressure. The heart, chest, and abdomen revealed nothing remarkable. Neurological examination showed marked spasticity and marked weakness of all extremities, most marked in the legs, with evidence of moderate muscular wasting. Attempts to passively move the legs elicited complaints of pain. There was generalized hypoesthesia over the entire body with anesthesia below the hips. The Romberg was positive with patient falling always to the left. There were typical striatal tremors of the hands and head, with fibrillary twitchings occurring over the face and occasionally observed in the arms. Of the reflexes the gag and corneal were both active, the biceps and triceps were active and equal, the knee jerks were bilaterally hyperactive, while neither abdominal nor ankle jerks could be obtained. The blood Wassermann test was negative; the red blood count was 4,800,000, the white count 6,320 with a normal differential. The spinal fluid showed initial pressure of 140 mm. of water with only one cell and normal Queckenstedt test. Spinal fluid Wassermann test was negative, as was the colloidal mastic. Roentgen-rays of the teeth showed extensive alveolar absorption. Roentgen-rays of the spine showed an extensive hypertrophic arthritis. An electro-encephalogram showed normal alpha rhythm.

The first week was spent in improving the patient's state of nutrition by forced feedings, intravenous fluids, extra vitamins, etc. The conjunctival infection was

cured, the decayed teeth were removed and a normal state of hydration was achieved. However, the patient remained blind, being unable to distinguish light from dark although the pupils reacted. Rotation of a lettered drum before his eyes failed to induce nystagmus. The motor and sensory changes persisted.

Intensive psychiatric therapy was started with daily interviews which included efforts to determine the causative factors, positive suggestive therapy, sub-convulsive dosages of metrazol given intravenously, etc. The patient rather rapidly improved on this therapy. His sight gradually returned, he became able to walk, the spasticity disappeared, the anesthesia disappeared and finally even the tremors disappeared. The disturbing situational factors were adjusted satisfactorily by conferences with the patient's family, and the patient returned to his home. He has remained well during the eight months he has been at home.

This case is enlightening. When first admitted, the more the patient attempted to control his disturbing symptoms by volitional effort—and he made honest efforts to do so on command—the worse these symptoms became. None of the many physicians who saw this patient could mimic the twitchings, the spasticity in flexion or the anesthesia which he presented. It might be argued that since he was cured by psychotherapy, the twitchings observed could not have been fibrillary. This, of course, is true, but it is not important. Several experienced neurologists examined this patient prior to efforts at psychotherapy, and agreed that the twitchings were fibrillary in nature. The usual tests for distinguishing an “hysterical” from an “organic” illness, such as the rotation of a lettered drum before the eyes to induce nystagmus, the Hoover's sign, etc., all pointed to an “organic” rather than an “hysterical” illness. There was argument among the physicians as to diagnosis which was only settled by the cure by psychotherapeutic methods. The patient had been a well-integrated individual without previous evidence of “hysterical” personality for 50 years prior to the development of this illness. No evidence of constitutional inadequacy could be found—unless one includes such factors as arteriosclerosis and arthritis as evidence of constitutional inadequacy. The illness was of such severe nature that it had resulted in muscular wasting, secondary infection and malnutrition, all increasing in severity so that had not some intensive therapy been undertaken, it seems quite likely that the patient might soon have died.

The psychopathologic factors included lowered capacity to adjust, due to arteriosclerosis and advancing age, the disturbing and incapacitating pain of arthritis, while the illness was precipitated by certain disturbing situational factors. No attempt has been made to discuss them completely or to elaborate on the finer details of the psychotherapeutic measures employed. It is only noted that they were present, they were altered by psychotherapeutic methods, including the chemotherapy of metrazol injections, and the patient was cured of his “hysterical” illness and was taught to live with his “physical” illness.

BIBLIOGRAPHY

1. CRISPELL, RAYMOND S.: Extramural and neuropsychiatry in a general hospital, South. Med. and Surg., 1940, cii, 105.

2. SADLER, WILLIAM S.: Theory and practice of psychiatry, p. 675, C. V. Mosby Co., St. Louis.
3. Ibid: p. 671.
4. Ibid: p. 666 and p. 669.
5. Ibid: p. 662.
6. HENDERSON, D. K., and GILLESPIE, R. D.: A textbook of psychiatry, Fourth Edition, p. 450, Oxford University Press.
7. Ibid: p. 459.
8. ROSANOFF, AARON J.: Manual of psychiatry, Seventh Edition, p. 1055, John Wiley & Sons, Inc.
9. Ibid: p. 627.
10. MENNINGER, KARL A.: The human mind, Second Edition, p. 383, Alfred A. Knopf.
11. COBB, STANLEY: Psychiatric approach to the treatment of epilepsy, Am. Jr. Psychiat., 1940, xcvi, 1009.
12. PIKER, P.: 1817 cases of suicidal attempt—a preliminary statistical survey, Am. Jr. Psychiat., 1938, xcv, 97.
13. NOYES, ARTHUR P.: Modern clinical psychiatry, Second Edition, p. 343, W. B. Saunders & Co.
14. BILLINGS, EDWARD G.: A handbook of elementary psychobiology and psychiatry, p. 120, Macmillan, New York.

CASE REPORTS

IDIOPATHIC HYPOPARATHYROIDISM; A REPORT OF 2 CASES *

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HYPOPARATHYROIDISM is a condition which the internist meets fairly commonly. It generally results from the inadvertent removal of one or more parathyroid glands in the process of thyroid operations, more rarely after the purposeful removal of one or more adenomatous or hyperplastic parathyroid glands to alleviate hyperparathyroidism.

The metabolic and chemical abnormalities of hypoparathyroidism were clearly defined by Albright and Ellsworth in 1929.¹ Since that time much has been added to our knowledge of the therapy for this condition; and an especially valuable recent addition to our therapeutic armamentarium is dihydrotachysterol (A. T. 10).^{2, 3, 4, 5, 18}

Very rarely one sees patients with hypoparathyroidism who have undergone no surgical procedures in the cervical region, and in whom the etiology of the parathyroid insufficiency is completely unknown. The group at the Massachusetts General Hospital⁶ has recently reviewed the literature on this condition and added six cases of their own. We were fortunate during the past year in having under our observation simultaneously two patients suffering from hypoparathyroidism of unknown etiology. The findings in both patients fulfilled all the criteria for this diagnosis as laid down by Albright and Ellsworth.¹ Each patient presented certain quite unusual features, and, in view of the great rarity of the condition, we have felt that a report of our observations was justified.

CASE 1

J. H., a 15-year-old school-boy, was first brought to the Harriet Lane Infirmary, of the Johns Hopkins Hospital in January, 1928 because of photophobia and excessive lacrimation. He was then 4 years old. His parents had noted that, ever since an attack of measles followed by whooping cough at the age of two years, light hurt the child's eyes, and that he protected them either by keeping them shut or by holding something over them.

Examination at that time showed a normally developed child. He persisted in keeping his eyes closed or covered. There was marked lacrimation, and when a glimpse of the conjunctivae could be obtained "small points of epithelial defects" were seen. A diagnosis of phlyctenular kerato-conjunctivitis was made. In addition it was noted that the hair on the head was thin and patchy, and that his eye-brows and lashes were sparse. The skin was dry, the teeth discolored and irregularly developed, the nails short and thickened. The tonsils were enlarged. In other respects the general examination was negative. The blood Wassermann reaction was negative,

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but the tuberculin test gave a positive reaction in a dilution of 1-100,000. Roentgen-ray of the chest was normal. Skin and hair changes were considered to be "multiple congenital ectodermal defects."

A tonsillectomy was performed, and during the next two years the patient was given tuberculin therapy, ultra-violet irradiation, and cod liver oil. There was complete disappearance of the kerato-conjunctivitis but no change in the photophobia or blepharospasm.

The patient was not seen again until December, 1937, when he was referred to the Wilmer Clinic by the school doctor because of persistence of the photophobia. In the interim he had been perfectly well in every other respect, participating normally in school activities and maintaining an average grade in his studies. Because of a suspected endocrine disorder, the patient was referred to the Medical Clinic. Toward the end of the physical examination the patient happened to bump into the examiner and his facial muscles were seen to twitch. Chvostek's and Trousseau's signs were then sought, and both were found to be positive. In another laboratory serum calcium was found to be 6.2 mg. per cent.

The patient's family history is entirely non-contributory. His mother and father are living and well as are also six siblings. There is no familial history of tuberculosis.

The patient's birth and development up to the age of 2 years were apparently perfectly normal. He had had chicken pox at the age of 18 months, measles and whooping cough at 2 years, as previously mentioned, and mumps when he was 2½ years old. Aside from the eye trouble and infrequent upper respiratory infections, his general health had been excellent. At no time had he ever had convulsions or complained of muscular cramps or paresthesias. Sweating had always been normal. There had never been any cough, stridor, or other respiratory symptoms. No history of gastrointestinal or urinary symptoms was obtained. In 1937 he fractured his right humerus playing base-ball, but this was the only history of any bone injury. The fracture healed normally.

Because of lack of coöperation on the part of the family, the patient was not seen again for nine months.

On September 27, 1938, he was persuaded to come to the Johns Hopkins Hospital for study. The abnormal physical findings at this time were confined chiefly to ectodermal structures. The skin was dry, coarse, and scaly. The hair was very thin and patchy on the head and absent in the axillary and pubic regions. The head was unusually long with prominent occipital and frontal bosses. The eye-lashes and eyebrows were scanty.

The appearance of the external surface of the lids may be seen in figure 1. Examination of the eyes was difficult because the lids closed spasmodically when attempts were made to examine them. A liberal dose of sedative and instillations of pontocain solution somewhat facilitated examination. There were no lesions on the palpebral or ocular conjunctivae or on the corneae, and consequently there was no apparent reason for the blepharospasm. Visual acuity was 20/20 O.U. The ocular fundi seemed normal and ophthalmoscopic examination failed to reveal opacities in the media. Slit-lamp examination revealed only lenticular changes. Small, white, irregularly-shaped opacities—for the most part subcapsular but also present in the outer cortex—were seen both anteriorly and posteriorly.

The teeth showed marked deficiency of enamel formation with delayed and irregular eruption of the deciduous teeth and retarded development of the permanent teeth (figure 2). The finger and toe nails were short, thick, and largely overgrown by skin (figure 3). There was a strongly positive Chvostek's sign, and Trousseau's sign was positive after the tourniquet had been applied 90 seconds. No other abnormalities were noted in the physical examination. The height was 155.6 cm., the span 154.6 cm., and his weight 48.2 kg. Blood pressure was 110 mm. of Hg systolic and

60 mm. diastolic. Laboratory data: Hemoglobin, red blood cells, and white blood cells were normal. Examination of the stool and urine showed no abnormalities. Non-protein nitrogen: 33 mg. per cent. Phenolsulphonphthalein excretion: 30 per cent in 15 minutes and 64 per cent in 2 hours. Urea clearance: 83 per cent normal maximum clearance. Blood Wassermann: negative. Serum calcium: 5.0 mg. per cent. Serum inorganic phosphate: 12.1 mg. per cent. Total serum protein: 7.1 gm. per cent (refractive index method). The blood was found to have a vitamin A con-



FIG. 1. Note sparsity of eye-brows and lashes and the thin, patchy scalp hair.

tent of 0.4 unit (lower limit of normal by the method is 0.7-0.8 unit). Clotting time: 18 minutes (normal: 6-12 minutes). Basal metabolic rate: plus 29 and plus 18 on two separate occasions, but the tests were not very satisfactory. The electrocardiographic record showed a levogram with low T_2 and prolonged QT interval but no other abnormalities.

Roentgen-ray reports: Heart and aorta normal. Lungs clear. Head: Normal skull. Intravenous pyelogram: Negative. Bone roentgen-rays: Bones of extremities, pelvis, and spine show increased density and sclerosis throughout (figure 4). Bone age as determined by roentgen-ray was normal.



FIG. 2. Note deficiency of enamel formation of incisor teeth.

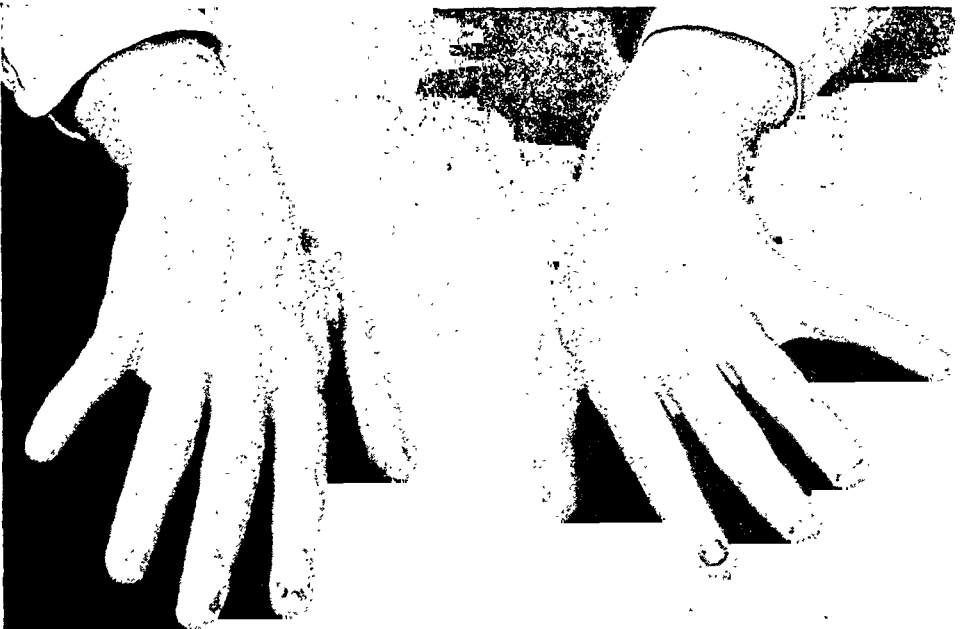


FIG. 3. Note rough, short, thick fingernails resembling somewhat the appearance in epidermophytosis.

Samples of the patient's fingernails were found to have a cystine content of 7.12 per cent by Dr. Sullivan of Georgetown University. This value was considered to be significantly below the normal value of 11 to 12 per cent.

Dental reports (November, 1938): "There has been much interference with the developmental processes of the dental organs. The enamel of the incisors and 6 year



FIG. 4. Note the greatly increased calcium deposit with normal bone architecture.

molar teeth, which is developed in the first year of life, is markedly hypoplastic, while that of the bicusps and 12 year molars (as seen by roentgen-ray) is more perfectly formed. There is gross malarrangement of the teeth of both arches, which is in all probability due to the disharmony between the exfoliation of the deciduous teeth and eruption of the permanent. This condition has proceeded to such an extent that several of the permanent are definitely impacted in bone and will either never erupt or will erupt far out of their normal position." (Figures 2 and 5.)

SPECIAL STUDIES

Chart 1 shows the results of the calcium and phosphate balance studies carried out. The periods are consecutive and each one represents the daily average of stool and urine analyses for five days. During the first period the patient was on a diet low in calcium and moderately high in phosphorus. He was barely able to maintain a positive calcium balance but showed a definite phosphorus re-

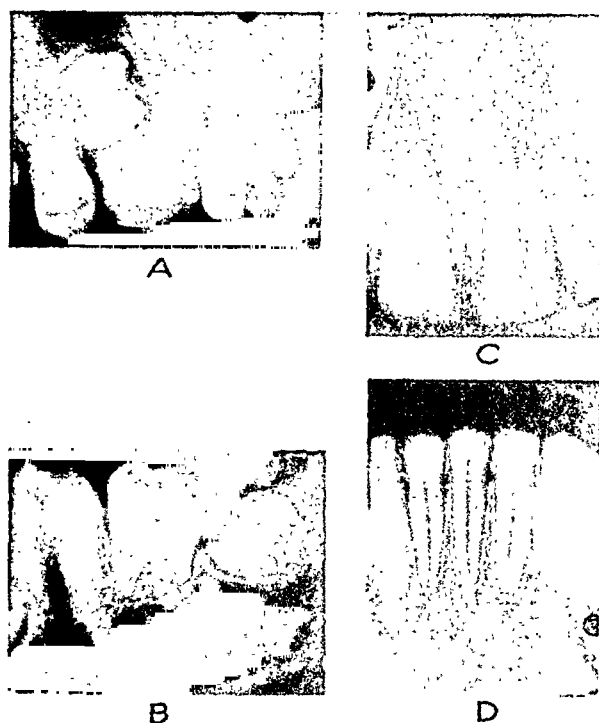


FIG. 5. *A* and *B*. Molar teeth. Note retardation of development and eruption as well as increased density. *C* and *D*. Incisor teeth. Note hypoplastic enamel at incisal edge and general lack of development as well as the increased density of the remainder of the tooth and also increased density of the mandible as evidenced by the increased prominence of the bony trabeculae.

CHART I

Calcium and phosphorus balance in case 1 on low calcium, normal phosphorus diet; high calcium, low phosphorus diet and with dihydrotachysterol therapy.

5 Day Periods	Calcium				Phosphorus				Serum		Therapy
	Urine gm. per day	Feces gm. per day	Intake gm. per day	Balance gm. per day	Urine gm. per day	Feces gm. per day	Intake gm. per day	Balance gm. per day	Ca mg. %	P mg. %	
1	.030	.088	.137	+.019	.422	.104	.741	+.215	5.2 (I)	13.3* (I)	
2	.029	.618	1.697	+.868	.192	.351	.349	-.194	5.3 (I)	12.5 (I)	
3	.029	1.256	1.697	+.230	.133	.223	.349	-.007	6.1 (V)	9.6 (V)	
4	.049	.846	1.697	+.620	.056	.259	.349	+.034	7.9 (V)	9.6 (V)	A.T. 10 3 c.c. for 3 days 1 c.c. for 2 days

* The Roman numerals indicate day of period on which blood sample was taken.

tention. In the second and subsequent period the diet was changed to one of high calcium (12 gm. added calcium lactate) and low phosphorus. The sharp rise in the calcium balance in the first five days following the dietary change was undoubtedly due to a lag in fecal excretion and equilibrium was not attained until the third five day period. It is noteworthy that during 10 days on a high calcium low phosphorus diet without other therapy there was a significant drop in serum phosphorus and rise in serum calcium, thus tending to corroborate the findings of Anderson and Lyall⁷ and Shelling,⁸ and confirming the importance of a low phosphorus diet in the treatment of hypoparathyroidism.^{9, 7, 14} It is probable that with the phosphorus content of the diet constant, raising the calcium intake alone will diminish the absorption of phosphorus and thus lower the serum phosphorus, as suggested by the experiments on rats of Shohl and his collaborators.²²

During the fourth period dihydrotachysterol was administered and, as has been found by other authors,⁴ there resulted a marked increase in the absorption

EFFECT OF DIHYDROTACHYSTEROL (A.T.10) ON THE SERUM CALCIUM AND PHOSPHATE LEVEL IN IDIOPATHIC HYPOPARATHYROIDISM (CASE I.)

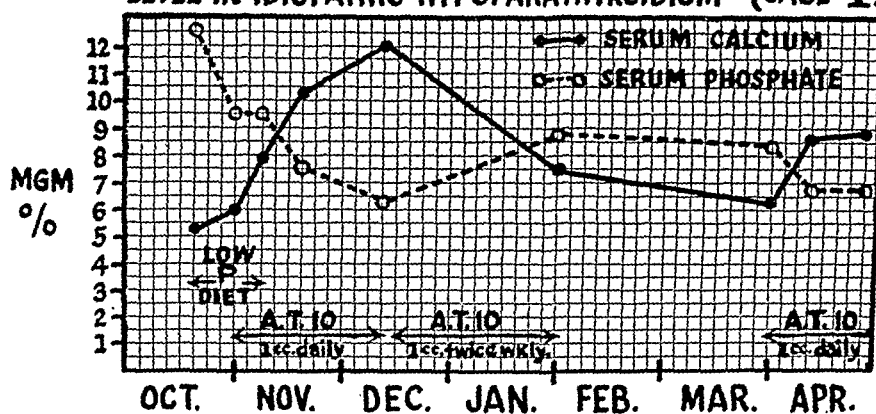


CHART 2. Showing the level of serum calcium and phosphorus and phosphatase as influenced by dihydrotachysterol therapy.

of calcium from the gastrointestinal tract with a coincidental rise in serum calcium. Contrary to the findings of others,⁴ however, there was a decrease in urinary phosphate excretion with no significant change in phosphate balance or serum phosphate level. Unfortunately, we were not able to continue the balance studies for more than a single five day period on dihydrotachysterol. Hence, we cannot say whether this effect of dihydrotachysterol on the phosphate balance was only a transient one, or whether it may have been related to the relatively small quantity of drug administered, to the low intake of phosphorus or to some other factor.

Chart 2 shows the effect of more prolonged administration of dihydrotachysterol on the serum calcium and phosphate level in patient 1. It will be noted that on a daily dose of 1 c.c. the serum calcium rose to 12.2 mg. per cent at the end of six weeks, while the serum phosphate fell to 6.3 mg. per cent. A dose of 1 c.c. twice weekly, however, was not sufficient to maintain normal serum calcium and phosphate levels. During this whole time the patient received 12 gm. of calcium lactate and 10 minims of oleum percomorph daily. The intake

of phosphorus was not restricted, however, and it is of some interest that the serum phosphate remained abnormally high even when the serum calcium level had risen to normal. At no time did the patient exhibit active tetany although Chvostek's and Trousseau's signs became positive whenever the serum calcium level was sufficiently depressed. During the period shown in chart 1 there was no significant variation in the total plasma protein level. Except for the disappearance of the signs of tetany and considerable decrease in the severity of the blepharospasm there had been little demonstrable change in the patient's general condition or in the ectodermal, osseous, or ophthalmological disturbances at the termination of this study. Subsequent to hospital discharge the patient was again lost to observation for awhile. In October, 1939 a general examination showed no essential deviation from his status in the fall of 1938. The appearance of the bones in roentgenograms was unchanged, the blepharospasm persisted, and serum calcium and phosphorus were essentially the same as before therapy. He stated that he had taken dihydrotachysterol very irregularly, not more than 75 days out of the year.

DISCUSSION OF CASE 1

That this patient's parathyroid glands were really underfunctioning and that there was not some sort of tissue resistance to parathormone seems proved by the vigorous response in urinary phosphorus excretion when parathormone was

CHART 3

Urinary excretion of phosphorus in case 1 before treatment, showing excretion of phosphorus in the response to 2 c.c. parathormone given intravenously. Compare control period which shows no increased phosphorus excretion after 2 c.c. normal saline intravenously.

Time	Control Period				Parathormone Test					
	Water Intake	Urine Volume c.c.	Urine P mg.	P/hr. mg.	Water Intake	Urine Volume c.c.	Urine P mg.	P/hr. mg.	Serum P mg. %	Serum C mg. %
7-8 a.m.	200	12	1.4	.023	200	58	22.3	.361		
8-9 a.m.	200	195	21.4	.357	200	112	24.5	.395		
9-10 a.m.	200	?	26.5	.434	200	218	21.6	.366	12.5	5.3
Normal saline 2 c.c. intravenously 10 a.m.					Parathormone 2 c.c. (200 units) intravenously					
10-11 a.m.	200	240	26.0	.474	200	182	82.0	1.344		
11-12 Noon	200	160	24.6	.432	200	170	109.0	1.786		
12-1 p.m.		150	25.8	.432		53	35.3	.631		
4 p.m.									11.0	6.9

given intravenously (chart 3). The procedure used in this experiment was identical with that previously used by us¹⁰ in testing patients' sensitivity to parathormone. It can be seen from the chart that this boy's fasting urinary excretion of phosphorus was approximately that of a normal person. In our

former studies¹⁰ it was found that in hypoparathyroid subjects the fasting urinary excretion of phosphorus was very low. We are not sure why in this case the urinary phosphorus was high, but it may have been due to the very high serum phosphate in this patient—none of our former patients having shown nearly so high a value. When parathormone was injected the urinary phosphorus excretion increased four-fold. This response is of the same order of magnitude as seen in normal persons, though of course their serum phosphate level is from 3 to 4 mg. per cent instead of 12 mg. per cent as in our patient.

At a later date the test was repeated at a time when serum phosphate was 9.2 mg. per cent. The fasting urinary excretion of phosphorus then averaged 4 mg. and increased to 60 mg. per hour after intravenous parathormone injection.

The skin, nail, and hair changes shown in this boy have been reported in other patients suffering with this disease. Just how such anomalies are brought about is unknown, but since they occur apparently in postoperative hypoparathyroidism also, they must be ultimately due to the deficiency of parathyroid hormone and not due to whatever may be the etiologic factor that destroys the function of the parathyroid gland in idiopathic hypoparathyroidism. Furthermore the cutaneous abnormalities have been reported to have disappeared entirely under appropriate therapy.¹² The teeth show the alterations in structure which have been emphasized by Albright as being characteristic of hypoparathyroidism in juvenile patients¹¹ and are similar to those described in parathyroidectomized young rats.^{19, 20, 23}

The finding of an abnormally low cystine content in the fingernails is of interest as indicating a disturbance in sulfur metabolism. Whether or not further studies along these lines may shed light on the nature of the ectodermal defects cannot be stated at the present time.

Excessive bone formation such as occurred in this boy has not, to our knowledge, previously been noted in this condition, though it is perhaps what might be expected. *Hyperparathyroidism* with its high urinary excretion of calcium and phosphorus, in the absence of an adequate calcium intake to maintain equilibrium, results in generalized rarefaction of the skeleton. *Hypoparathyroidism*, in the presence of a high calcium and phosphorus intake as was true in this case, might reasonably be expected to show bones denser than normal. Since, from the history, it seems fair to assume that deficient parathyroid function had been present in this boy since the age of two and probably since birth, one may conclude that his osteoid tissue was laid down and calcified in a medium far higher in phosphorus and lower in calcium than normal. Dr. Edwards A. Park, on seeing our patient, recalled some of his experiments on rats which had been fed low calcium and high phosphorus diets. The bones of these rats seemed structurally normal but exceedingly dense—quite like those of our patient. After seeing our patient, Dr. Fuller Albright has recently reexamined the bones on several of his juvenile patients with idiopathic hypoparathyroidism and found the bones to be of increased density in all of them.¹¹

CASE 2

C. R., a 56-year-old unmarried school teacher entered the Phipps Psychiatric Clinic on May 29, 1938 because of an agitated depression. She had had two previous depressive episodes; the first in 1906 lasted only a few months, the second began in 1930. At this time, because of menorrhagia, the pelvic organs were irradiated with

subsequent cessation of the menses but with very minor vasomotor menopausal phenomena. There was no apparent effect of this artificial menopause upon the depression which deepened and lasted about 18 months with gradual recovery.

From 1932 until her present illness began she had seemed her usual self and had carried out normally her duties as school teacher. During the winter of 1937-38 she had seemed more irritable and to have less interest in her work. On April 15, 1938 an explosion occurred in a refrigerator tank at the school. Ammonia fumes escaped in large amounts. The patient remained calm despite pandemonium among the children, saw all her pupils removed from the building in orderly fashion and then left the building herself. She is said to have fainted momentarily after her own exit, but recovered promptly and went home unassisted. Observers stated that there were no convulsive or tetanic manifestations at this time.

The following day, because of feelings of great nervousness and tension dating from the time of the explosion, the patient went to a Turkish bath establishment. After a brief period in a steam cabinet she suddenly developed carpopedal spasm, contractile pains in the intercostal and abdominal muscles, and difficulty in breathing. This attack lasted about 20 minutes with gradual release of the severe spasticity. But the symptoms never entirely disappeared and returned in severe form several times again before her admission to the hospital. There was almost constant "breathing difficulty and congestion of the nasal passages" which was attributed to the irritation of the ammonia fumes.

She continued to be highly nervous and in the two weeks immediately prior to her admission there was an acute return of her depressive symptoms with frequent crying spells. On May 2 the patient's eyes were examined because she was having trouble with close work. A refractive error was found but her ophthalmologist writes: "The lenses were entirely clear."

Her past history revealed little else of interest. She had been known to have a dorsal scoliosis since childhood but never suffered with any symptoms from it. The dietary history revealed no abnormalities. She had always eaten much fruit and green vegetables, ate meat once daily, and drank on an average 400 c.c. of milk daily.

On admission to the Phipps Clinic on May 29, 1938 the patient was in a highly excitable agitated state. General physical examination revealed only the following abnormal findings: Gross tremor of the extended fingers, involuntary twitchings of the brachial and thoracic muscles, and a positive Chvostek's sign. Laboratory examinations: Hemoglobin 13.8 gm.; red blood cells 4.64 millions; white blood cells 5,000. Sedimentation rate 31 mm. Smear and differential count were normal; no eosinophilia was present. Non-protein nitrogen 36 mg. per cent; fasting blood sugar 112 mg. per cent. Wassermann reaction negative. There was a bare trace of albumin but no other abnormality in the urine examination.

Skeletal roentgen-rays were interpreted by Dr. John Pierson: "Moderate demineralization of all the bones." (Figure 6.)

On May 31, 1938, two days after admission, the record shows a serum calcium determination of 10 mg. per cent. In the light of previous and subsequent events the correctness of this calcium determination seems open to question. No inorganic phosphate or serum protein evaluations were made at this time.

Course in Hospital. The curious cyclical alterations in behavior during the early part of her hospital stay have been made the subject of a separate communication by Richter.¹³ Because of the development of active tetanic manifestations in mid-August, serum calcium and phosphate determinations were made. The calcium value proved to be 5.0 mg. per cent and the phosphate 8.7 mg. per cent. Phosphatase activity 1.2 Bodansky units. The course of her serum calcium and phosphorus values and anti-tetanic therapy may be seen on chart 4.

Soon after admission the patient's vision began to diminish and the development of cataracts was spectacularly rapid. When we were first privileged to see the pa-

tient in the latter part of October she was almost totally blind. At this time her antitetanic therapy consisted of 2 grams of calcium chloride three times per day given in the form of 40 per cent solution. The tetany was under good control. Because of some observations on appetite in deficiencies,¹² dihydrotachysterol was not admin-



FIG. 6. Decreased density of the spine.

istered until the middle of November. The usual rise in serum calcium followed its use. The drug was omitted during the period of recovery from the operation for removal of the cataracts. Thereafter it was resumed at 1 c.c. daily and has been continued at this level ever since, with the addition of varying amounts of calcium lactate. Serum calcium and phosphorus have been essentially normal for the past 9 months to the time of this writing, and there have been no further manifestations of tetany. Her psychiatric status improved steadily.

The patient was discharged from the hospital the latter part of January 1939 and led an inactive life at home almost entirely free of symptoms until her return in May, 1939 for a check-up examination. At this time, though alert and coöpera-

tive, she seemed to have a curious playful diffidence about answering questions directly. Since she flatly refused to be seen by any members of the psychiatric staff, a competent evaluation of her psychiatric status was impossible. She complained only of continued stiffness and soreness of all the muscles of her body but not to any incapacitating degree. She looked quite well. The general physical examination

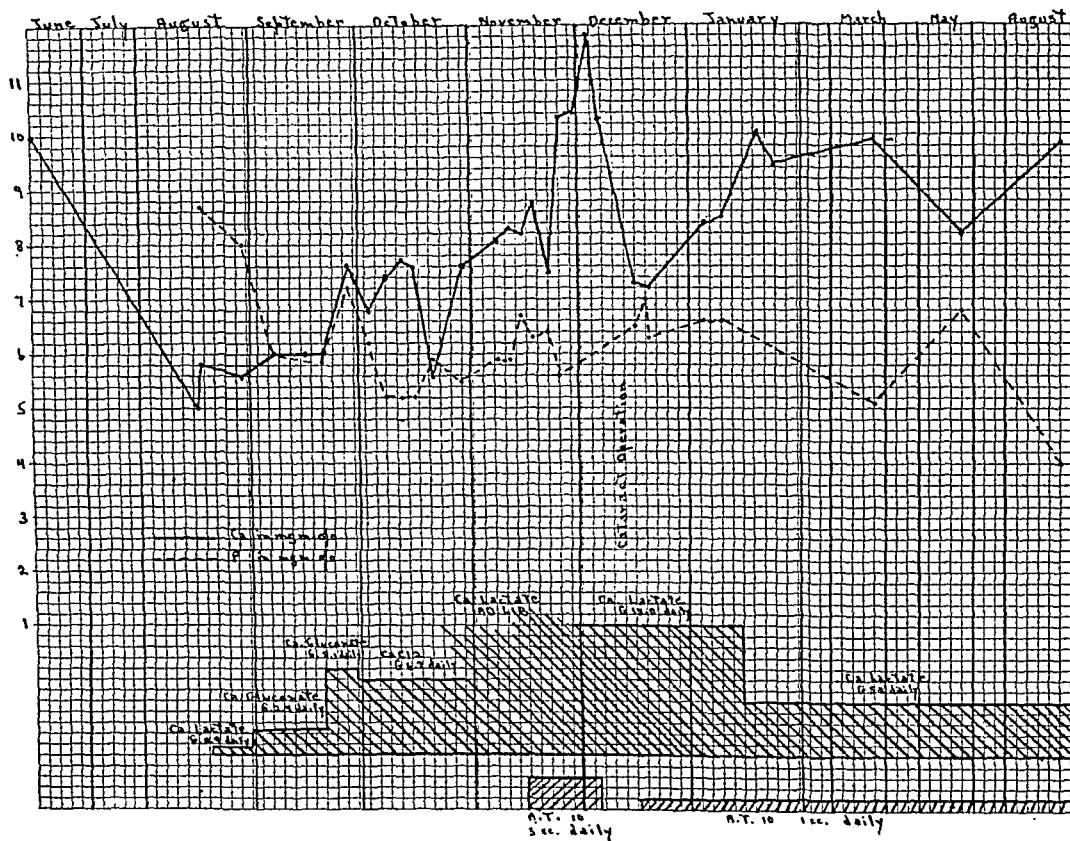


CHART 4. Course of serum calcium and serum phosphorus in case 2 as influenced by calcium therapy and administration of dihydrotachysterol.

proved to be normal with the exception of signs of mild hypertrophic arthritis, which was the reason for her aches and pains in the opinion of Dr. George Eaton, the orthopedic consultant. Chvostek's and Trousseau's signs were absent. Dr. Elliott Randolph, who performed the cataract operations, found the eye status to be entirely satisfactory from the point of view of operative result. Laboratory studies showed the blood morphology to be normal. Serum calcium was 8.2 mg. per cent, phosphate 6.8 mg. per cent, protein 6.9 gm. per cent. Phosphatase 1.5 Bodansky units. Stool and urine examinations were normal and the urinary calcium excretion was low when tested with Sulkowitch's solution.¹⁵ Roentgen-rays showed no change in the density of the bones from the previous examinations. During this admission the patient's sensitivity to parathormone was tested and the response in urinary phosphate excretion was found to be normal.

She left the hospital after these studies were completed, spent an uneventful summer at home, and has resumed her school duties in the fall of 1939. As can be seen from chart 4, with a normal diet, 1 c.c. dihydrotachysterol and 5 gm. calcium lactate per day, her serum calcium and phosphorus have remained essentially normal, and she has been entirely free of tetanic manifestations.

DISCUSSION

There are certain features of this case history that are worthy of discussion, though most are of a purely speculative nature. The most arresting feature is the abrupt onset of tetany within 24 hours after an exciting incident in which there was exposure to a heavy concentration of ammonia fumes. The most conservative interpretation would be that the patient had had mild hypoparathyroidism prior to the explosion incident. Physical fatigue and emotional disturbances are known to make worse the clinical manifestations of hypoparathyroidism. This has been the experience of many previous observers. But when one goes into the patient's past history one finds nothing suggestive of muscular cramps, spasms, or paresthesias, even though she had experienced a severe agitated depression previously. Furthermore the extraordinarily rapid development of bilateral cataracts under observation speaks for an acute disease process. Could the ammonia fumes have played any rôle? We have no clue as to any possible effect on the parathyroid glands of ammonia inhalation but hope to test this hypothesis with some laboratory experiments in the near future. As pointed out by the Massachusetts General Hospital workers,⁶ the etiology of idiopathic hypoparathyroidism in youthful patients and elderly patients may be quite different, but in both groups is entirely unknown at the present time.

The status of this patient's skeleton is also of interest. There seemed, by roentgen-ray, to be a general rarefaction of the entire bony structure, but most conspicuous in the bones of the spine. One wonders if perhaps there had been previously present *hyperparathyroidism* with subsequent burning out of the process leaving a deficiency of the internal secretion of the parathyroids. There were, however, no symptoms in her past history suggestive of hyperparathyroidism, and her intake of calcium had always been of such generous proportions as to make it doubtful if skeletal rarefaction would have occurred from moderate hyperparathyroidism. There was no history of vitamin D deficiency. To us the most likely explanation of the skeletal rarefaction is senile osteoporosis. This process, which appears to be a marked reduction in osteoblastic activity, is most commonly seen in women several years after the menopause. Our patient had a menopause artificially induced with radium eight years before she was first seen here. Her serum phosphatase activity was quite low, which would not be out of accord with such a diagnosis. Our impression is, then, that she had senile osteoporosis slowly developing over a course of seven years and an acute recent onset of hypoparathyroidism. It will be interesting to observe the effect of the hypoparathyroidism on the osteoporotic process for, as shown in the previous case of this report, hypoparathyroidism in itself tends to make for excessive bone formation.

Cataracts have been frequently described in association with hypoparathyroidism. However, the rapidity of development and the degree of density of such cataracts vary widely. The physiologic disturbance in hypoparathyroidism which is directly concerned with the cataract formation is entirely unknown, but since identical cataracts occur in association with other diseases in which the serum calcium is lowered but the phosphorus not raised,²¹ one would conclude that the low serum calcium level was in some way responsible. It should be emphasized that minimal alterations in the lens may be overlooked; hence examination with the slit-lamp is essential if the incidence of changes in the lens

as a result of parathyroid deficiency is to be estimated accurately. Frequently only a few months' time is required for the development of changes in the lens sufficient to destroy useful vision, as in case 2, whereas in other instances, as in case 1, after many years of hypoparathyroidism only minimal changes can be detected. Perhaps elderly patients tend to develop cataracts more rapidly than juvenile patients, given similar degrees of parathyroid deficiency. The majority of cataracts seen in diseases with low serum calcium are similar to those seen in diabetes and myotonic dystrophy. They are characterized by the subcapsular distribution of the opacities. Vogt described them as linear or fiber-like opacities on the cortex.¹⁶ Other observers¹⁷ have described diffuse or even nuclear changes. As such cataracts develop, the appearance changes until the entire lens may become a gray-white mass. In one of our postoperative hypoparathyroid patients wide clefts were apparent, similar to those of dinitrophenol cataracts. It is of interest that of four postoperative hypoparathyroid patients treated over a period of five years with oral calcium chloride therapy, which produces a mild acidosis, no lens changes were visible even with slit-lamp examination. Though the tetanic symptoms were entirely under control in these patients the serum calcium level rarely rose above 7.5 mg. per cent. The only known treatment for hypoparathyroid cataracts is surgical. To our knowledge restoration of the blood chemical status to normal has never caused reversion of the lens changes.

SUMMARY

Two cases of idiopathic hypoparathyroidism are reported. In the first, a young boy, the disease may have been of congenital origin; in the second the symptoms of tetany occurred abruptly for the first time following an explosion of a refrigerating plant in which the patient was exposed to ammonia fumes. In the juvenile patient roentgen-rays of the bones showed them to be of far greater density than normal and we have evidence to believe that dense bones are the rule in juvenile hypoparathyroid patients. The elderly patient showed greatly decreased bone density and it was thought that she suffered from so-called senile osteoporosis in addition to hypoparathyroidism. Lenticular changes were present in the juvenile patient to only a very slight degree though the disease process had been present many years; the elderly patient developed cataracts under observation with extreme rapidity.

In both patients the sensitivity to parathormone was tested and found normal, showing the disease to be a deficiency of parathormone rather than an increased resistance to it.

BIBLIOGRAPHY

1. ALBRIGHT, F., and ELLSWORTH, R.: Studies on the physiology of the parathyroid glands; calcium and phosphorus studies on a case of idiopathic hypoparathyroidism, *Jr. Clin. Invest.*, 1929, vii, 183.
2. HOLTZ, F.: Die Behandlung der postoperativen Tetanie, *Arch. f. klin. Chir.*, 1933, clxxvii, 32.
3. (A) MACBRYDE, C. M.: The treatment of parathyroid tetany with dihydrotachysterol, *Jr. Am. Med. Assoc.*, 1938, cxi, 304.
(B) MACBRYDE, C. M.: The treatment of hypoparathyroidism with dihydrotachysterol, *South. Med. Jr.*, 1938, xxxi, 720.
4. ALBRIGHT, F., BLOOMBERG, E., DRAKE, T., and SULKOWITCH, H. W.: A comparison of the effects of A.T.10 (dihydrotachysterol) and vitamin D on calcium and phosphorus metabolism in hypoparathyroidism, *Jr. Clin. Invest.*, 1938, xvii, 317.

5. ALBRIGHT, F.: Note on the management of hypoparathyroidism with dihydrotachysterol, *Jr. Am. Med. Assoc.*, 1939, cxii, 2592.
6. DRAKE, T. G., ALBRIGHT, F., BAUER, W., and CASTLEMAN, B.: Chronic idiopathic hypoparathyroidism; report of six cases with autopsy findings in one, *ANN. INT. MED.*, 1939, xii, 1751.
7. ANDERSON, I. H., and LYALL, A.: The treatment of chronic hypoparathyroidism, *Quart. Jr. Med.*, 1939, viii, 209.
8. SHELLING, D. H.: Calcium and phosphorus studies: effect of calcium and phosphorus of diet on tetany, serum calcium and food intake of parathyroidectomized rats, *Jr. Biol. Chem.*, 1932, xcvi, 195.
9. ELLSWORTH, R.: Observations on a case of postoperative hypoparathyroidism, *Bull. Johns Hopkins Hosp.*, 1933, lii, 131.
10. ELLSWORTH, R., and HOWARD, J. E.: Studies on the physiology of the parathyroid glands. VII. Some responses of normal human kidneys and blood to intravenous parathyroid extract, *Bull. Johns Hopkins Hosp.*, 1934, lv, 296.
11. ALBRIGHT, F.: Personal communication.
12. CANTAROW, A., STEWART, H. L., and MORGAN, D. R.: Chronic idiopathic parathyroid tetany, *Endocrinology*, 1939, xxiv, 556.
13. RICHTER, C. P., HONEYMAN, W., and HUNTER, H.: Behavior and mood cycles apparently related to parathyroid deficiency, *Jr. Neur. and Psychopath.* (to be published).
14. ELLSWORTH, R.: Diagnosis and treatment of parathyroid underfunction, *Internat. Clin.*, 1933, iii, 27.
15. BARNEY, J. D., and SULKOWITCH, H. W.: Progress in the management of urinary calculi, *Jr. Urol.*, 1937, xxxvii, 746.
16. VOGT, A.: *Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges*, Zweiter Teil, 1931, Julius Springer, Berlin, 553-556.
17. O'BRIEN, C. S.: The cataract of post-operative tetany, with report of three cases, *Arch. Ophth.*, 1932, vii, 71.
18. SNAPPER, I.: The treatment of tetany, *Lancet*, 1934, i, 728.
19. ERDHEIM, J.: Ueber den Kalkgehalt des wachsenden Knochens und des Callus nach der Epithelkörperchenextirpation, *Frankf. Ztschr. f. Path.*, 1911, vii, 175, 238, 295.
20. TOYOFUKU, T.: Ueber die parathyreoprive Veränderung des Rattenzahnes, *Frankf. Ztschr. f. Path.*, 1911, vii, 249.
21. HOESCH, K.: Katarakt und Nebenschilddrüsenepilepsie, *Deutsch. med. Wchnschr.*, 1937, lxiii, 1582.
22. BROWN, H. B., SHOHL, A. T., CHAPMAN, E. E., and ROSE, C. S.: Rickets in rats. XIII. The effect of various levels and ratios of calcium to phosphorus in the diet upon the production of rickets, *Jr. Biol. Chem.*, 1932, xcvi, 207.
23. SCHOUR, I., CHANDLER, S. B., and TWEEDY, W. R.: Changes in teeth following parathyroidectomy; effects of different periods of survival, fasting, and repeated pregnancies and lactations on incisor of rat, *Am. Jr. Path.*, 1937, xiii, 945.

CALCINOSIS UNIVERSALIS *

By J. FLETCHER LUTZ, M.D., F.A.C.P., *York, Pennsylvania*

THE abnormal deposition of calcium in the body has received considerable attention and study on the part of clinicians, biochemists, dermatologists, and roentgenologists. Instances of abnormal deposition of calcium may be divided into three main groups: progressive myositis ossificans, metastatic calcinosis, and calcinosis (subdivided into calcinosis circumscripta and calcinosis universalis).

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Progressive Myositis Ossificans. Mair¹ defines the disease as one of the locomotory system in the growth period of children, affecting not only the muscles but tendons, ligaments, fasciae, and aponeuroses. It is very commonly associated with various congenital abnormalities, the commonest being malformation of the great toes. There is no ossification of muscle but an ossification of fascia and a transformation of fibrous tissue into bone in which ligaments and muscle tendons may participate. The ossification spreads along the fibrous septa and along the tendons, commencing at the bone and extending superficially. The first case was reported by Munchmyer² in 1869. Helfrich³ in 1879 described this rare disease and showed the great prevalence of microdactyly and the absence of the last phalanx of the great toe in 75 per cent of cases. Rosenstirn,⁴ who reviewed the literature extensively, also found this deformity very prevalent.

Metastatic Calcinosis. This is a peculiar deposit of calcium found in the heart, lungs, kidneys, and other organs. It does not affect the muscles, fasciae, or subcutaneous tissues. In this condition there is usually a hypercalcemia which is probably of endocrine origin and attributed to the parathyroids.

Calcinosis. Weber⁵ in 1878 reported the first case of calcinosis. Verse⁶ in 1912 reported a case which he called calcinosis universalis. Steinitz⁷ divides the cases of calcinosis into two groups: calcinosis circumscripta and calcinosis universalis. *Calcinosis circumscripta* is the deposit of calcium in the subcutaneous tissue and usually attacks the hands and feet primarily. It rarely occurs in children. *Calcinosis universalis* is the deposit of calcium in the subcutaneous tissue, the muscles, and sometimes along the nerve trunks, especially in the extremities. The hands and feet are not often involved and the number of deposits tends to decrease from the trunk towards the hands and feet. This disease is frequently encountered in children and may be seen even in the first six months of life. In collecting cases of all ages in the literature Steinitz found only 34 cases of calcinosis universalis. It is this extremely rare condition—calcinosis universalis—with which this article is primarily concerned.

Bauer, Marble, and Bennett⁸ studied calcinosis universalis extensively and found there was no evidence of any of the unusual abnormalities which are known to produce pathological calcification; namely, chronic inflammation, infarction, hemorrhage, or tissue necrosis. The earliest abnormality noted was the deposition of finely divided calcium particles around the periphery of fat cells, which otherwise histologically appeared to be normal. No evidence of "calcium binding substances within degenerated areas" was seen, since calcification appeared in areas of fat before there was any microscopic evidence of degeneration. The calcium when first retained may have combined with fatty acids but, if so, did not remain in this form, as the analysis of one of these deposits showed that all the calcium could be accounted for as calcium carbonate or tertiary calcium phosphate. They agreed with the conclusion of others that inflammatory changes are not causative factors in these deposits; they considered it reasonable to conclude that calcium and phosphorus metabolism are abnormal in these rare cases of calcification; and they suggested that the increased retention of calcium and phosphorus may be the result of a local cellular condition as yet undetermined. These views relating to the metabolic disturbance in this disease are contrary to the views of Tisdall and Erb,⁹ and of Wilens and Derby.¹⁰

LABORATORY DATA
York Hospital, February 6, 1934—March 8, 1934

Date	Blood Chemistry					Hematology							Urine					Miscellaneous					
	Non-Fasting Blood Sugar, Mlg. %	Fasting Blood Sugar, Mlg. %	Blood Serum Phos-phorus, Mlg. %	Blood Serum Calcium, Mlg. %	CO ₂ Combining Power, Vol. %	Sedimentation Index, Mm.	HGB, % of Normal (Sahli)	RBC Millions	WBC	Differential WBC, % of Total				Color	Reaction	Sp. G.	Alb.	Sugar	Microscopic Findings	Electrocardiogram	Basal Metab.	Spinal Fluid	Kahn Test
2/ 6/34							68	3,510	11,700	70	26	1	3	Straw	Acid	1.002	Neg.	Neg.	Few squamous cells, mucous shreds and amorph. sed.				
2/ 7/34*						27	58	2,970	13,450														Neg.
2/ 8/34	195.2	111.1	2.97	24.8																	-2 (Check -10)		
2/ 9/34																				Nothing abnormal	+9 (Check +9)		
2/12/34										10	90											U. 3 Ca 10 WBC 90% Polys. 10% Lymph.	
2/13/34				24.2	50																		Ca 8.4 Mlg. %
2/19/34†				21.5																			Ca 10. Mlg. %
2/23/34				23.8																			
3/ 8/34				20.1																			

* Cervical smear showed no gonococci.

† Mantoux negative.

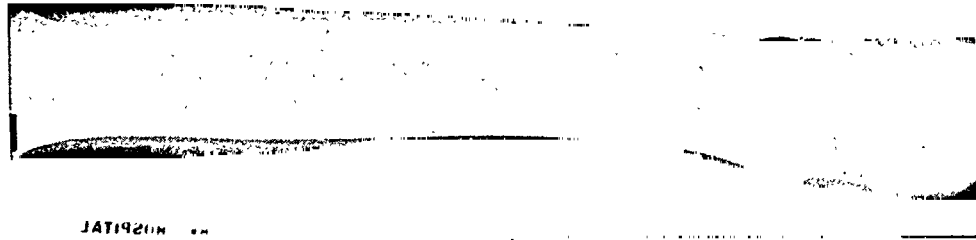


Fig. 2. (February 7, 1934). Roentgenogram of right leg showing extensive deposit of calcium with normal bone structure.

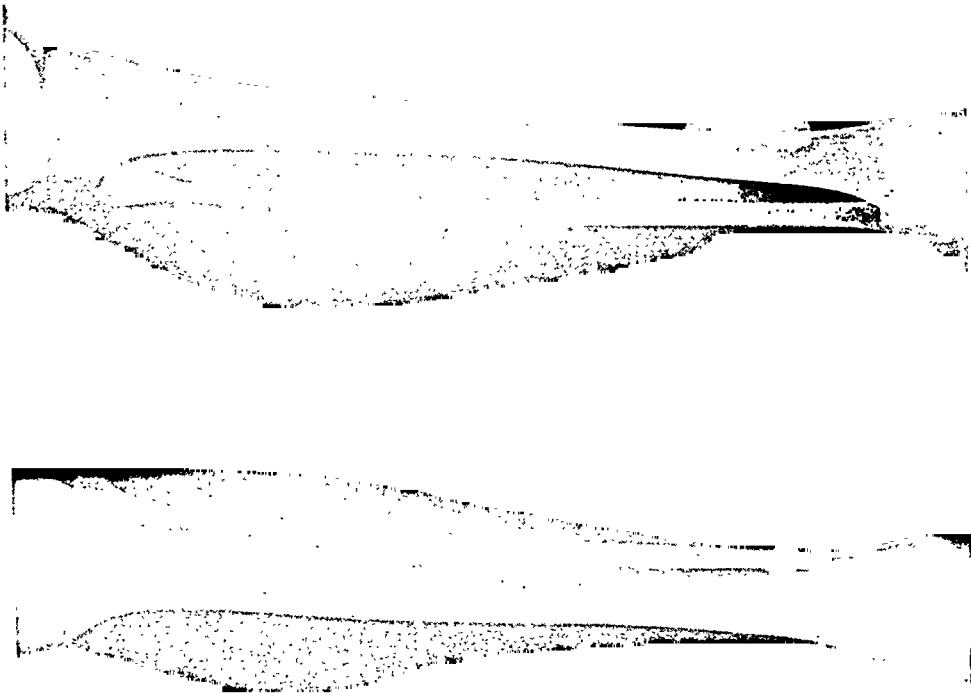


Fig. 1. (February 7, 1934). Roentgenogram of left leg showing deposit of calcium with normal bone structure.

They reasoned that the normal blood values for calcium and phosphorus were not in favor of a metabolic disorder.

Langmead¹¹ studied the relationship of calcinosis and scleroderma, dermatomyositis and myositis fibrosa, and believed that scleroderma and dermatomyositis are almost inseparable, and that universalis calcinosis is probably a subsequent development.



FIG. 3. (February 7, 1934.) Roentgenogram of right foot and ankle showing deposit of calcium with normal bone structure.

Durham¹² studied the relationship between scleroderma and calcinosis and found that calcinosis was not limited to any one type of scleroderma and that local inflammatory changes are usually not a causative factor, in that the composition of these deposits was calcium phosphate and carbonate, while uric acid was never found. Chemical studies do not indicate any constant variation in either the whole blood or the serum values. There is no oversaturation of calcium salts as is thought to occur in metastatic calcification. Durham states: "It is no-wise clear whether calcinosis with scleroderma results from local metabolic alterations or deranged inorganic metabolism. As in other types of pathologic calcification the colloidal proteins are thought to play a prominent part."

Litchwitz calls attention to the possible part proteins may play in the induction of calcification. He thinks that the precipitation of colloids in degenerated tissue may bring about a reduction in soluble crystalloids, whereby the more insoluble salts, such as calcium, are precipitated.

Wells¹⁴ pointed out that the calcium is deposited in areas in which carbon dioxide is least abundant.

ONSET OF THE DISEASE

Skossogorenko¹⁵ reported a case of a patient who gave the history of some kind of infection during the latter part of 1922, with high temperature, and who five months later began to "swell." This swelling was "dropsy-like" and

began about the pelvis and femur, spreading uniformly over the entire body. The skin was edematous and pitted. This general edema lasted for three years and was accompanied by diffuse pains, and the patient was unable to move the limbs.



FIG. 4. (February 7, 1934.) Roentgenogram of right foot showing small deposit of calcium with normal bone structure.

Craig and Lyall's¹⁶ case presented the following history: A girl aged five years, three months, was admitted to the hospital on March 25, 1927, on account of palpable lumps in the legs. In February 1926, she developed swelling of the legs from below the ankles to above the knees. No redness was noted in the skin, but the swelling was accompanied by some pain. The joints were a little

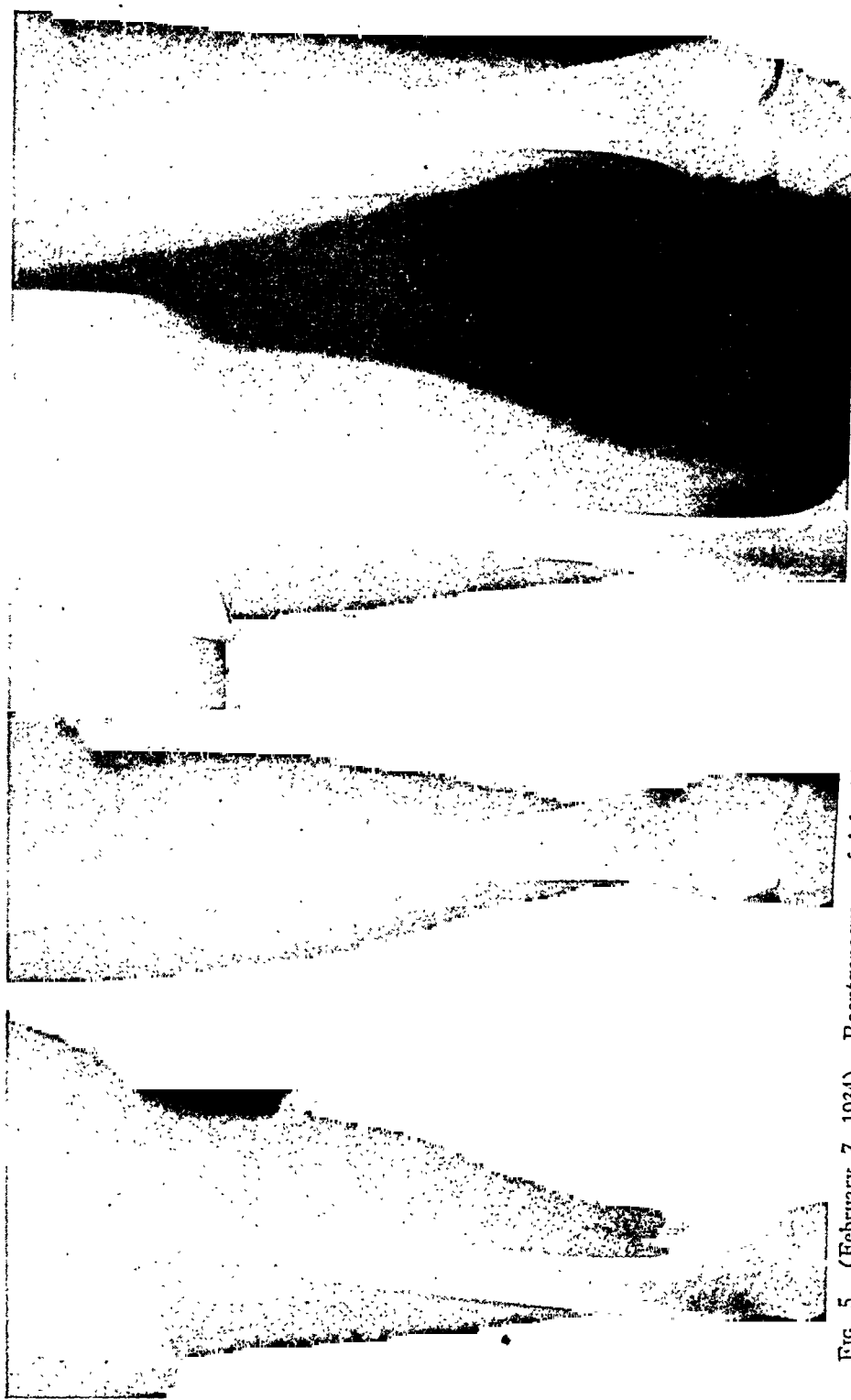


FIG. 5. (February 7, 1934). Roentgenogram of left thigh showing a large nodule of calcium and small deposit with normal bone structure.

FIG. 6. (February 7, 1934). Roentgenogram of right thigh showing extensive deposit of calcium with normal bone structure.

stiff, but there were no pains when they were moved. The swelling lasted three months, and then slowly subsided.

Kennedy¹⁷ reported instability and difficulty in walking for two years preceding the onset of calcium deposits.

Logan¹⁸ described a similar case in which Raynaud's syndrome was a prominent feature.

A number of cases have been reported in the literature which are associated with scleroderma, notably those of Durham and Kennedy.

The onset of the disease shows a wide variation, but it is definitely shown that it is more common in children, though it may also be found in the aged. The essential features are acute illness followed by muscular weakness and calcium deposits.

PATHOLOGY

Microscopically, the tissue shows a marked infiltration of calcium arranged in globules of varying sizes. The connective tissue is swollen and edematous. Often the calcium salts lie only between the fat cells. The fat cell inside is entirely empty. The endothelium of the vessels is frequently conspicuous and bulges into the lumen. The vessels may show considerable fibrosis of the walls, and some of them may be occluded by this fibrous tissue. The bulk of the lime salt was observed in the fat and fibrous tissue. No giant cells are present and no bone formation. In more advanced cases dense collagenous fibrous tissue, in which calcareous particles are embedded, has replaced the adipose tissue.

DIAGNOSIS

The diagnosis is not difficult when the roentgen-ray is employed, and the findings are definitely pathognomonic of the disease. The calcium is distributed throughout the subcutaneous tissue. There is no evidence of the bone involvement, which is so pronounced in parathyroid dysfunction. The symptoms naturally will depend upon the location of the calcium deposits. It quite frequently happens that the calcium nodules ulcerate through the skin, leaving a sinus which is very slow in healing. The general health of the individual may become affected because activities are limited by the mechanical disturbance which results from the stiffening of the muscles with the calcium salts. Pain may be pronounced when there is pressure on the nerve trunks.

PROGNOSIS

Prognosis is rather unfavorable so far as cure is concerned, and the disease is very progressive. Only one recorded case has gone to autopsy, reported by Durham, the patient having died from some other disease. There was no pathologic change in the parathyroids, though the disease had existed for 37 years.

TREATMENT

Treatment is of little avail. Nothing has ever been found to benefit this condition. The disease generally continues to progress. Craig and Lyall claimed beneficial results from di-sodium phosphate. Kennedy advised a ketogenic diet. Skossogorenko recommended that ammonium chloride be adminis-

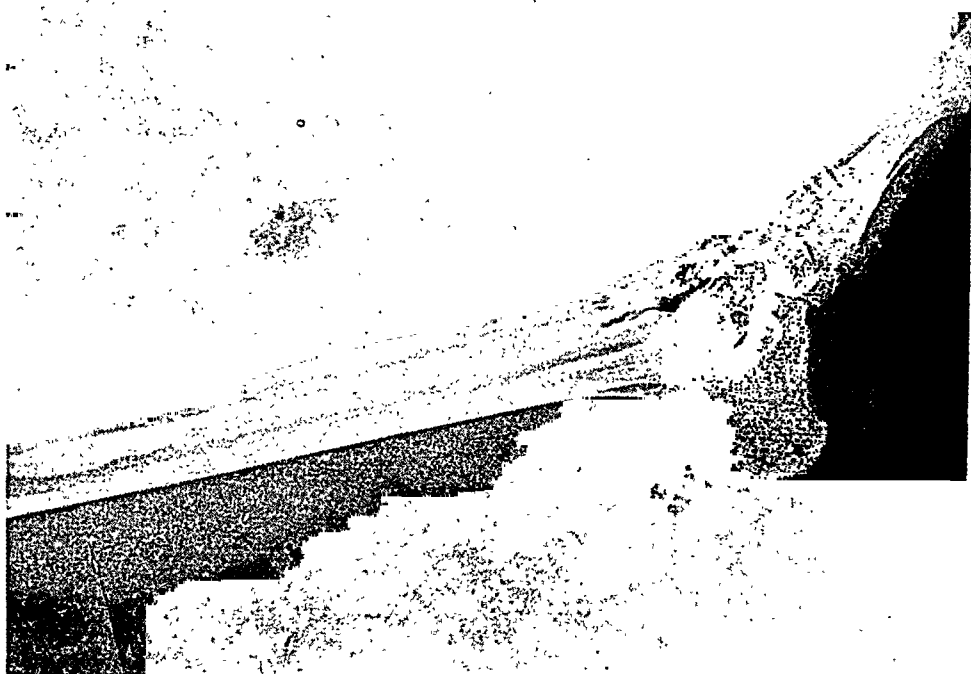


FIG. 7. (March 3, 1934). Roentgenogram of right leg and foot showing no change in deposit of calcium following treatment.



FIG. 8. (May 7, 1934). Roentgenogram of right leg after biopsy showing slight reduction in density of calcium formation, especially in the region of the ankle.

tered internally, with Bier's hyperemia. Hein¹⁹ employed heliotherapy and claimed beneficial results. Parathyroid extract has been used without satisfactory results.

The following case is reported as one of calcinosis universalis:

CASE REPORT

H. S., aged 16 years, female, school child, white, American.

Chief Complaint. Patient was admitted to the Surgical Dispensary of the York Hospital, York, Pennsylvania, on January 16, 1934, exhibiting an ulcer, about 3 cm. in diameter, on the left leg, situated about 8 cm. above the ankle on the outer aspect. There was definite swelling in the lower right leg and also pain in both legs, more especially the right. At this time the patient was referred to the Metabolic Dispensary for more complete studies.

Past Personal History. Customary childhood diseases; occasional attacks of nocturia; menstruation began at 15 years; periods regular, lasting four to six days; present weight is her best weight.

Family History. Father and mother living and well. Patient had four brothers, three living, one having died of pneumonia. There is no history of deformities, dwarfism, or physical abnormalities, and no history of carcinoma, tuberculosis, renal or heart disease, or epilepsy.

Present Illness. The patient fell on the left hip in 1930. The hip became "very sore," and after a year began "draining." It discharged for six months, after which it stopped and the sinus healed. On January 9, 1934, a small ulcer developed on the right knee.

Physical Examination. The patient was admitted to the York Hospital Ward for observation, study, and treatment on February 6, 1934. She was found to be a well-developed, well-nourished girl of 16 years, weight 90 pounds; no pallor; general appearance good. Temperature 99.8°, pulse 80, respirations 20. General examination was negative except for the lower extremities: On the left hip there was a scar of the injury; the left leg presented two ulcers, one above the knee and one on the anterior third of the leg; the right leg presented several ulcers. They were somewhat indurated and were covered with brown scabs. The measurements of the two extremities were apparently the same.

Laboratory findings on admission to the Metabolic Dispensary, January 16, 1934: Non-fasting blood sugar 136 mg. per 100 c.c.; fasting blood sugar 106 mg. per 100 c.c.; urine, acid, sp. gr. 1.008, albumin and sugar absent, microscopic findings essentially negative; Kahn test negative. Blood: red blood cells 2,840,000; white blood cells 18,950; hemoglobin 50 per cent. Differential: transitionals 2 per cent, eosinophiles 1 per cent, polymorphonuclears 76 per cent, lymphocytes 3 per cent, mononuclears, 9 per cent, basophiles 1 per cent, myelocytes 8 per cent.

The following report of biopsy tissue from right leg (April 27, 1934) was made by Dr. Howard M. Jamieson, former pathologist of the York Hospital:

"The specimen consists of three small pieces of firm pinkish white tissue, which together measure 1.0 by 0.5 cm. in size. The tissue as a whole is markedly fibrous and shows numerous small pin-point sized granules of white calcareous material, some of which are merely lying on the surface, and others embedded in the tissue. Gross section shows most of these granules to be on the surface, very few of them being near the center of the masses. All of these granules can very easily be separated from the tissue, giving the impression that they have been merely deposited in their present situations, rather than formed here.

"*Microscopic examination* shows fibrosed muscular tissue and fascia, with



FIG. 9. Photomicrograph of section of subcutaneous tissue removed at biopsy, showing calcareous particles embedded in dense collagenous fibrous tissue. (Made by the late Dr. J. C. Bloodgood.)

numerous small areas of calcification. These areas are all well demarcated and there is no calcium inside the cells, indicating a deposit rather than a formation in situ. Some of these areas are surrounded by zones of fairly dense, small, round-celled infiltration of the chronic irritational type. No true inflammatory change can be seen, and careful search does not reveal any evidence of new bone formation. The condition is one of calcification and not ossification.

"In addition to the above, there was also received about 4.0 c.c. of thick white milky fluid, closely resembling rather thin plaster of Paris, shortly before it sets. Microscopic examination of an emulsion of this fluid shows a few crystals of the phosphate type. Chemical examination shows the fluid to be almost entirely calcium phosphate (about 95 per cent), with traces of chlorides. Fluoroscopic examination of the fluid shows it to be opaque to roentgen-rays.

"From the above microscopic and chemical findings, one must conclude that this is a case in which, due to faulty metabolism, there is a rich deposit of calcium salts, almost entirely phosphate, in the muscle fascia and the more superficial layers of the muscle itself, but no true ossification, and no bone formation of neoplastic type."

Diagnosis: Calcinosis universalis.

Roentgenologic Findings. The patient was referred for the first roentgenological examination on February 7, 1934. The preliminary examination was made of both legs, followed by the examination of the entire body. The right leg shows extensive deposits of calcium extending from the head of the fibula downward along its anterior and external aspects and dorsal aspect of the foot, with a few nodules in the region of the phalanges of the first, fourth, and fifth toes. Two nodules were seen in the lower third of the left leg. In the region of the middle third of the right thigh, in the subcutaneous tissue, there was a rather diffuse deposit of calcium present. Several nodules were seen in the middle third of the left thigh. The bony structure throughout the entire body showed no evidence of decalcification, and there was no deviation from the normal bony structure. No deposits were seen in the abdominal organs.

Roentgenological Diagnosis: Calcinosis universalis.

Roentgenological examination of the right leg and foot made on March 3, 1934 shows no material changes in the calcium deposits. The roentgenological examination made of the right leg and foot on May 7, 1934, after biopsy, shows some reduction in the density of the calcium deposits.

The fluoroscopic examination showed that the fluid which was collected at the time of biopsy was opaque to the roentgen-ray.

Treatment. The patient was given 50 grains of ammonium chloride three times a day, without any noticeable change in the calcium deposit. She was discharged on June 15, 1934. The ulcer which had been present on the legs had healed but at the time the patient left the Hospital, the wound, in the region of the site from which the biopsy had been taken, continued to discharge. The patient returned to the Surgical Dispensary for dressings, and was last seen July 10, 1934. The wound at that time had not entirely healed. The patient failed to return to the Hospital for further treatment after this date.

SUMMARY

Calcinosis universalis should be recognized as a definite clinical, pathological, and roentgenological entity.

The disease consists of the deposit of calcium in the subcutaneous tissue and muscle with reactive fibrosis.

A large percentage of the cases are associated with scleroderma.

The majority of the cases reported show a normal blood calcium.

The roentgenological findings are typical of the disease, which consists of the deposit of calcium in the subcutaneous tissue and muscle, the principal location being in the extremities. There are no bone changes such as are characteristic of hyperparathyroidism.

The disease is probably the result of a disturbance of calcium metabolism. It is progressive but not necessarily fatal. The treatment has not been satisfactory.

REFERENCES

1. MAIR, W. F.: Myositis ossificans progressiva, *Edinburgh Med. Jr.*, 1932, xxxix, 13, 69.
2. MUNCHMYER: Ueber Myositis ossificans progressiva, *Ztschr. f. rat. Med.*, 1869, p. 9.
3. HELFRICH, quoted by MAIR, W. F.: Myositis ossificans progressiva, *Edinburgh Med. Jr.*, 1932, xxxix, 13, 69.
4. ROSENSTIRN, JULIUS: Myositis ossificans progressiva, *Ann. Surg.*, 1917, 485.
5. WEBER, H.: Sklerodermie, *Korrespbl. Schweiz. Ärzte*, 1878, xx, 623.
6. VERSE, M.: Ueber Calcinosis universalis, *Beitr. z. path. Anat. u. z. allg. Path.*, 1912, liii, 212.
7. STEINITZ, H.: Calcinosis circumscripta (Kalkgicht) und Calcinosis universalis, *Ergebn. d. inn. Med. u. Kinderh.*, 1931, xxxix, 216.
8. BAUER, W., MARBLE, A., and BENNETT, G. A.: Further studies in a case of calcification of subcutaneous tissue (calcinosis universalis) in a child, *Am. Jr. Med. Sci.*, 1931, clxxxii, 237.
9. TISDALL, F. F., and ERB, I. H.: Report of two cases with unusual calcareous deposits, *Am. Jr. Dis. Child.*, 1924, xxvii, 28.
10. WILENS, G., and DERBY, J.: Calcification of subcutaneous tissue in a child (calcinosis universalis), *Am. Jr. Dis. Child.*, 1926, xxxi, 34.
11. LANGMEAD, F. S.: The relationship between certain rare diseases: generalized scleroderma, calcinosis, dermatomyositis, myositis fibrosa, *Arch. Pediat.*, 1923, xi, 112.
12. DURHAM, R. H.: Scleroderma and calcinosis, *Arch. Int. Med.*, 1928, xlii, 467.
13. LITCHTZWITZ, L.: Ueber die Bedeutung der Kolloide für die Konkrementbildung und die Verkalkung, *Deutsch. med. Wchnschr.*, 1910, xxxvi, 704.
14. WELLS, H. G.: Metastatic calcification, *Arch. Int. Med.*, 1915, xv, 574; *Trans. Chicago Path. Soc.*, 1914-1915, ix, 208.
15. SKOSSOGORENKO, G. F.: Calcinosis interstitialis universalis, *Jr. Bone and Joint Surg.*, 1932, xiv, 339-345.
16. CRAIG, JOHN, and LYALL, ALEXANDER: A case of calcinosis universalis and a suggested method of treatment, *Brit. Jr. Child. Dis.*, 1931, xxviii, 29.
17. KENNEDY, R. L. J.: Calcinosis and scleroderma in a child treated by ketogenic diet, *Med. Clin. N. Am.*, 1929, xii, 1655.
18. LOGAN, J. R.: Unusual calcareous deposits in the soft tissue of the hands, *Arch. Radiol.*, 1923-24, xxviii, 55; *Lancet*, 1923, 900.
19. HEIN, BARNEY J.: Calcinosis universalis, reprinted from *Arch. Surg.*, 1933, xxvi, 389-396.
20. HANSON, A. M.: Physiology of the parathyroid, *Jr. Am. Med. Assoc.*, 1935, cv, 113-114.
21. BEATH, R. M.: A case of calcinosis universalis with premature senility, *Brit. Jr. Radiol.*, 1934, vii, 372-374.
22. BOLAM, MASON: Calcinosis with report of a case of calcinosis universalis, *Brit. Jr. Dermat.*, 1935, xlvi, 562-563.
23. RUDOLPH, COUNCILL C.: Calcinosis universalis and dermatomyositis, *Jr. Pediat.*, 1934, iv, 342-351.

PNEUMOPERITONEUM FOLLOWING USE OF THE FLEXIBLE GASTROSCOPE*

By LEON SCHIFF, M.D., F.A.C.P., RICHARD J. STEVENS,† M.D.,
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PERFORATION of the stomach is said to occur very infrequently following the use of the flexible gastroscope. According to Schindler and Renshaw,¹ this accident is known to have occurred five times in a total series of four thousand examinations carried out independently by Henning, Gutzeit, Moutier, Benedict, Schloss, and Schindler. In every instance an instrument with a "sponge tip" was used, and in none was the outcome fatal.§ In two instances the stomach itself was reported to be "apparently normal," and recovery occurred without surgical intervention. In Schindler's own experience perforation has occurred in three cases of gastric carcinoma. The perforations, however, involved portions of the stomach wall not invaded by the growth, were twice located high on the posterior wall, and once on the anterior wall near the greater curvature. As he was able to see the peritoneum in two of these cases, he believed that in these the perforations were caused by the tip of the instrument and were not due to overdistention of the stomach with air.

In a study dealing with various factors influencing perforation of the stomach with the flexible gastroscope, Schindler and Renshaw conclude that the tip of the instrument is the most important. They showed experimentally that with the "sponge tip" there is greater friction on the stomach surface and the pressure of the advancing gastroscope is, therefore, more apt to be localized to the stomach wall in contact with the tip. On the other hand, "a long rubber finger directs the instrument in the line of least resistance and initiates bending of the flexible portion thereby distributing pressure on the stomach surface more evenly." They therefore advise the universal use of a rubber finger tip 4 to 6 cm. in length. However, even with the use of such a tip, pneumoperitoneum may result as evidenced by the following case report.§

CASE REPORT

Clinical History: R. B., white male, aged 77, was admitted to the Cincinnati General Hospital, March 16, 1938, because of dyspnea and weakness. In 1929 he was found to have hypochromic anemia with achlorhydria. Although symptomatic improvement followed liver therapy at that time, there was no reticulocyte increase.

Physical Findings: He was somewhat underweight and was suffering with a mild senile psychosis. The sclerae were not jaundiced. There was marked pallor of the conjunctivae. The papillae of the tongue were prominent. The lungs were emphysematous. The heart was moderately enlarged to the left, and a systolic murmur was heard at the apex. The blood pressure was 170 systolic and 100 diastolic.

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† Justin A. Rollman Fellows in Internal Medicine, 1938-1939, and 1937-1938, respectively.

‡ Bergh, Bowers, and Wangenstein² mention one instance of perforation in their clinic. Their patient developed pneumoperitoneum without evidence of peritonitis and recovered without operation.

§ This represents the only recognized instance of perforation in our experience which includes more than five hundred examinations.

The upper border of the liver was at the fifth intercostal space in the mid-clavicular line; the edge was two fingers'-breadth below the right costal margin in the mid-clavicular line. The spleen was not felt. Appreciation of vibration was decreased in the lower extremities. There was minimal edema of both ankles.



FIG. 1. Film of chest made March 19, 1938, two days prior to gastroscopy.

Laboratory Findings: Hemoglobin 4.2 gm. per 100 c.c.; red blood count 2,830,000; white blood count 7,800; hematocrit 20; mean corpuscular volume 71. The urinalysis was normal. Chemical tests of the stools for blood were negative. Following histamine there was no free hydrochloric acid in the gastric secretion. The blood Kahn test was negative.

On March 19, 1938, a roentgenogram of the chest was taken which showed "only moderate enlargement of the cardiopericardial shadow." The diaphragm appeared normal (figure 1).

On March 21, 1938, after the patient had had nothing to eat or drink for 12 hours, gastroscopic examination was done with the flexible Wolf-Schindler instrument with a rubber, finger-like tip measuring 4.8 cm. in length. (Twenty minutes before the examination he had received a hypodermic injection of morphine sulfate gr. $\frac{1}{6}$ and atropine sulfate gr. $\frac{1}{150}$.) The instrument was readily passed. The patient coöperated excellently. The stomach was inflated with air in the usual manner. The pylorus was normal. There was pallor of the mucosa. The rugae were absent. Numerous branching vessels were seen in the body of the stomach. It was evident that diffuse atrophic gastritis was present. Visibility was excellent throughout the entire examination. The peritoneum was not seen, nor was there any sudden defla-

tion of the stomach as Schindler has observed in perforation of the stomach wall by the instrument.³ Incidentally, a finger-like projection was seen to dip into the antrum in the direction of the pylorus (figure 2). It was at first believed to represent a benign polyp but was found to be the end of the instrument itself when it was covered

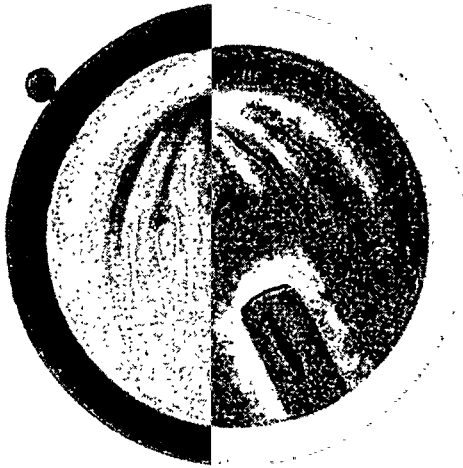


FIG. 2. Photograph of drawing showing tip of instrument mistaken for benign polyp in antrum.

with a strip of adhesive and passed into another patient. The tip had become extremely flexible and had probably been bent upon itself.

After two hours had elapsed following completion of the gastroscopic examination, the patient was permitted to eat the regular hospital diet and take fluids as desired. Part of the day was spent up and about the ward. There were no subjective complaints. His temperature was normal. A white count on March 23 was 10,000. On March 25, four days after the gastroscopic examination, he was sent to the roentgen-ray department for a gastrointestinal series.[†] No barium was given as Dr. H. Senturia, on preliminary fluoroscopy, noticed that there was a layer of air about 1½ cm. in depth under each dome of the diaphragm (figure 3). The patient was immediately returned to the ward and examined. The abdomen was flaccid and free of tenderness. There was some reduction of liver dullness. He offered no complaints. The white blood count was 7,600 with a normal differential count. He was seen in consultation with Dr. Max Zininger who advised against surgical intervention. A bland meat-free puréed diet was prescribed, and the patient was allowed to get out of bed as desired.

One month later a gastrointestinal roentgen-ray series was negative. At this time there was no demonstrable air below the diaphragm. His red blood count had risen to normal after oral administration of iron, and he was discharged on May 5, 1938. He has been followed in the out-patient department, and, when last seen on March 13, 1939, he was feeling quite well.

Whether the pneumoperitoneum was due to the instrument penetrating the stomach wall or to overdistention of the stomach with air, was, of course, not

[†] Ordinarily gastroscopic examinations are carried out after previous roentgen-ray examination of the gastrointestinal tract. This order was reversed in this case, because, in another patient barium was still present in the stomach four days after it had been given and had prevented a satisfactory gastroscopic examination.

established.* The stomach wall was probably thinner than normal because of atrophy of the mucosa. More pressure than usual was probably exerted on the posterior wall of the stomach near the greater curvature as evidenced by the fact that the tip of the instrument was bent upon itself. However, there was no



FIG. 3. Film of chest made four days after gastroscopy, showing free air below diaphragm.

deflation of the stomach nor was the peritoneum seen as might have been expected had the instrument itself penetrated the stomach wall.

The accidental discovery of the pneumoperitoneum is remarkable. This suggests that this complication may occur more frequently than is generally believed. It is possible that the absence of pain may have been partly due to the hypodermic injection which preceded the examination. Failure of peritonitis to develop in spite of the ingestion of food and water soon after the gastroscopic examination is deserving of comment, as is the patient's spontaneous recovery.

Of much interest in this connection is the report of Bergh, Bowers, and Wangenstein² who found that in a group of 29 experimental animals the mortality following perforation of the empty stomach was only 6.9 per cent. In their earlier studies water was withheld for 24 hours and food for 48 hours after the perforations were produced, but in later studies the animals were al-

* Since this paper was submitted, RUMBALL, J. M., in the *Jr. Am. Med. Assoc.*, 1939, cxiii, 2053, has reported perforation of the jejunum with a flexible gastroscope equipped with a rubber finger-tip.

lowed to take food and water at will. On the other hand, when the stomach contained food at the time of perforation, the mortality rose to 86.7 per cent.

SUMMARY

Pneumoperitoneum may follow the use of the flexible gastroscope with the finger-like rubber tip. It may develop in the absence of any symptoms, may be unaccompanied by any signs of peritonitis, and may disappear without surgical intervention in spite of the administration of food and water shortly after withdrawal of the instrument.

A case is described which marks the seventh* reported instance of perforation of the stomach following use of the flexible gastroscope. As in the other reported cases, the outcome was not fatal.

BIBLIOGRAPHY

1. SCHINDLER, R., and RENSHAW, J. F.: Experimental study with certain tips used on the Wolf-Schindler flexible gastroscope, *Am. Jr. Digest. Dis. and Nutr.*, 1936, iii, 747-751.
2. BERGH, G. S., BOWERS, W. F., and WANGENSTEEN, O. H.: Perforation of the gastrointestinal tract: an experimental study of factors influencing the development of peritonitis, *Surgery*, 1937, ii, 196.
3. SCHINDLER, R.: Personal communication to the authors.

* Since this paper was submitted, SCHINDLER, R., in *Am. Jr. Digest. Dis.*, 1940, vii, 293-295, has reported eight instances of perforation of the stomach, one of perforation of the jejunum, and one of perforation of the esophagus following use of the flexible gastroscope.

EDITORIAL

THE LIVER AND ESSENTIAL NUTRIENT FACTORS

It has long been recognized by experimental workers and clinicians that the liver can be protected against the action of hepatotoxic agents and the consequences of biliary obstruction by dietetic means. The optimal diet commonly prescribed for patients who have hepatic disease is high in carbohydrate and low in fat; the protein requirements are made up largely from vegetable sources, eggs and milk. The high carbohydrate content, of course, is intended to favor storage of glycogen and the low fat content to prevent excessive deposition of fat within the liver. It has been demonstrated that meat protein and its extractives seem to exert an unfavorable effect on the injured liver but recognizing the need for an adequate intake of protein, other sources have been drawn on to maintain nitrogen equilibrium. It may be assumed that a qualitative difference exists between various proteins as far as their effect on the liver is concerned; in fact, experimental evidence indicates that under certain conditions protein may function in a protective manner. To date, no studies have been reported on the possible effects of specific amino acids contained in animal protein as contrasted to those derived from vegetable sources, whites of eggs and milk; perhaps some amino acids have a specific protective effect on hepatic cells and others exercise an opposite influence.

Recent studies indicate that other basic requirements are probably of considerable importance and must be met in order to maintain normal hepatic structure. Rich and Hamilton¹ reported that cirrhosis of the liver developed among rabbits maintained on a diet of synthetic composition and without any natural sources of the vitamin B complex. Similar hepatic lesions also were observed when thiamin chloride, riboflavin, pyridoxine hydrochloride, nicotinic acid and vitamin E were added to the diet in quantities sufficient for normal maintenance. Further studies by these investigators revealed that an adequate amount of yeast added to the diet prevented the development of this type of cirrhosis and that increasing the amounts of the aforementioned components of the vitamin B complex had a partially protective effect. They concluded that some factor in yeast is necessary for prevention of pathologic change in the parenchyma of the liver of rabbits at least. In their recent report they called attention to the observations of György and Goldblatt,² who demonstrated that hepatic necrosis develops in rats maintained on a diet deficient in yeast. The specific substance in yeast which produces this effect has not yet been identified.

Choline also may exert some protective effect of a peculiar nature on the

¹ RICH, A. R., and HAMILTON, J. D.: Further studies on cirrhosis of the liver produced by a dietary deficiency, *Trans. Assoc. Am. Phys.*, 1940, *lv*, 133-139.

² GYÖRGY, P., and GOLDBLATT, H.: Hepatic injury on nutritional basis in rats, *Jr. Exper. Med.*, 1939, *lxx*, 185-192.

liver. Best and his co-workers ^{3, 4, 5} investigated this matter thoroughly and in a long series of experiments revealed that an adequate intake of choline prevents fatty metamorphosis of the liver which ordinarily occurs in animals maintained on a high fat diet; they further demonstrated that the deposits of fat in the liver, which followed intoxication with carbon tetrachloride, were removed more rapidly when choline was added to the diet of experimental animals than was the case in a series of control animals.

Griffith and Wade ^{6, 7} during the past year published additional reports on the effect of deprivation of choline. In observations made on rats they found that a deficiency of choline, in addition to producing a fatty liver, also arrested growth and caused regression of the thymus gland, splenomegaly and enlargement and hemorrhagic degeneration of the kidneys. Small amounts of choline prevented all the pathologic picture except deposition of fat in the liver. They also noted that the addition of cystine to the diet increased requirements for choline and that methionine had an opposite effect. From the foregoing, it is apparent that choline acts under some dietary conditions as a protective substance for the hepatic parenchyma and that its activity may be affected by the presence of certain specific amino acids.

Clinical evidence to support these observations has not been supplied to date but there is much to suggest that the patient who has alcoholic cirrhosis suffers not only from the hepatotoxic effect of alcohol but also from an actual dietary deficiency, the exact nature of which is not yet definitely known but which may involve some component of the vitamin B complex. Treatment directed toward correcting the latter condition by an optimal diet and generous supplies of the vitamin B complex has been productive of surprisingly good results in certain cases.

The matter of secondary deficiency in essential nutrient factors also has been studied in connection with hepatic disease. Good evidence indicates that the liver is a great storage depot for vitamins and perhaps for provitamins; its normally high content of vitamins A and D is well known, as is the fact that it is one of the principal storehouses for vitamin C. It likewise stores the vitamin B complex or at least certain portions of it. It is natural to suppose that in advanced hepatic disease a state of deficiency in respect to one or more of these vitamins may develop.

So far as the fat soluble vitamins are concerned, it is well known that night blindness may develop in the course of hepatic disease. As Patek ⁸

³ BARRETT, H. M., BEST, C. H., MACLEAN, D. L., and RIDOUT, J. H.: The effect of choline on the fatty liver of carbon tetrachloride poisoning, *Jr. Physiol.*, 1939, xcvi, 103-106.

⁴ BEST, C. H., CHANNON, H. J., and RIDOUT, J. H.: Choline and the dietary production of fatty livers, *Jr. Physiol.*, 1934, lxxxi, 409-421.

⁵ MACLEAN, D. L., RIDOUT, J. H., and BEST, C. H.: Effects of diet low in choline on liver function, growth and distribution of fat in the white rat, *Brit. Jr. Exper. Path.*, 1937, xviii, 345-354.

⁶ GRIFFITH, W. H., and WADE, N. J.: Some effects of low choline diets, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 188-190.

⁷ GRIFFITH, W. H., and WADE, N. J.: Choline metabolism. I. The occurrence and prevention of hemorrhagic degeneration in young rats on a low choline diet, *Jr. Biol. Chem.*, 1939, cxxxi, 567-577.

⁸ PATEK, A. J., JR., and HAIG, C.: Occurrence of abnormal dark adaptation and its relation to vitamin A metabolism in patients with cirrhosis of the liver, *Jr. Clin. Invest.*, 1939, xviii, 609-616.

has shown, the defect is not a matter of deficiency of vitamin A alone, for sufficient vitamin A to correct nyctalopia of patients without hepatic injury is ineffectual against night blindness in cirrhotic patients. Furthermore, the provitamin beta-carotene is also ineffective. The latter indicates that the difficulty probably lies in the inability of the liver to manufacture vitamin A from sources in which it is normally supplied to the body. A somewhat similar condition exists in respect to vitamin D. As Heymann⁹ has demonstrated, rats poisoned with carbon tetrachloride and maintained on a rachitic diet required enormous doses of vitamin D to correct the bony changes present. It is also known that patients who have cirrhosis of long standing may develop deficiency of vitamin D which manifests itself as osteoporosis; in extreme cases this condition may be sufficient to produce actual osteomalacia with pathologic fractures. For such patients a high intake of vitamin D and calcium is neither protective nor curative. In regard to the fat soluble, antihemorrhagic vitamin K, the evidence is even more striking. When hepatic damage has reached an advanced stage, neither the vitamin itself nor its synthetic analogues can be utilized in the formation of prothrombin. This fact has been demonstrated fully by both clinical¹⁰ and experimental¹¹ studies.

Knowledge in regard to deficiencies in the water soluble vitamins is considerably more meager. True deficiency of vitamin C is rare in hepatic disease, although low levels of cevitamic acid in the urine and plasma may be encountered occasionally. Such specific deficiency states as cheilosis, pellagra and peripheral neuritis are also decidedly uncommon. Some recent clinical evidence indicates that hepatic insufficiency, especially that which is associated with hepatic coma, may be due to a deficiency of thiamin chloride and nicotinic acid; at least, patients in coma have sometimes been miraculously revived by administration of these substances.

Certain obvious therapeutic implications arise from a consideration of the experiments described. The first is that certain types of dietary deficiency must be considered as playing an etiologic rôle in laying the groundwork for hepatic injury; the second is that hepatic disease, once it is present, renders the affected person liable to secondary deficiency of vitamin D. This is apparently more likely to involve the fat soluble compounds. It must be recalled that our clinical knowledge of specific deficiencies arising from failure of utilization of certain portions of the vitamin B complex, notably choline, is far from complete and that the influence of certain amino acids on the liver has yet to be ascertained. The problem is one of increasing complexity and yet in its solution may be the clue to some of the unsolved problems in the clinical physiology of the liver.

ALBERT M. SNELL.

⁹ HEYMANN, WALTER: Importance of the liver for the antirachitic efficacy of vitamin D, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 812.

¹⁰ BOLLMAN, J. L., BUTT, H. R., and SNELL, A. M.: The influence of the liver on the utilization of vitamin K, *Jr. Am. Med. Assoc.*, 1940, cxv, 1087-1090.

¹¹ FLYNN, J. E., and WARNER, E. D.: Prothrombin levels and synthetic vitamin K in obstructive jaundice of rats, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 190-194.

REVIEWS

The Rectum and Colon. By E. PARKER HAYDEN, A.B., M.D., F.A.C.S., Assistant in Surgery in the Harvard Medical School, Boston, Mass., Assistant Surgeon and Chief of Rectal Clinic, Massachusetts General Hospital, Boston, Mass. 434 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1939. Price, \$5.50.

This short book on the rectum and colon is written in a form that amounts to a series of monographs based on cases seen at the Massachusetts General Hospital Clinic and in the author's private practice. Because of this it tends to be rather incomplete in its discussion of certain conditions that are not prevalent in the Boston area, such as lympho-pathia venerea and the rarer disease entities in which the series from such a single source are bound to be small. However, most sections are quite complete and well written. The sections on anatomy and methods of examination are particularly good. The author's discussion of the treatment of hemorrhoids deserves attention. He gives one of the few good recent reports comparing the operative with the injection methods. He reaches the following conclusion: "Since that time (1928) there has been a gradual rise in the number of cases operated upon as our early hopes with regard to permanent results of injection treatment became modified." I feel that this statement is typical of most people's experience with the new wave of injection methods and solutions. So many people seem to think that injection is something new and a cure all, when really it is a mere recrudescence of a very old and several times discarded procedure. There is no question in anybody's mind concerning the author's statement that "Small and moderate sized uncomplicated internal piles giving symptoms of bleeding alone, or bleeding and protrusion with spontaneous retraction, are best suited to this method of treatment." The trouble is that too few people who use the method are capable of making this differentiation, or because of the *apparent* ease and safety of injection they do not attempt to make it. This is a very timely and carefully analyzed report with good follow-up of the patients treated by both methods.

In the field of major operative procedures on the right side of the colon and the segment of bowel between the recto-sigmoid junction and the anal margin the author seems to favor two-stage operations much more than is the case in certain other sections of the country. Not quite enough space comparatively, seems to be given to the major operations on the colon, together with the pre- and post-operative care of such patients.

J. C. O.

Diseases of Infancy and Childhood. By the late L. EMMETT HOLT, M.D., and JOHN HOWLAND, M.D., Revised by L. EMMETT HOLT, JR., M.D., and RUSTIN MCINTOSH, M.D. Eleventh Edition. 1421 pages; 25 × 17 cm. D. Appleton-Century Co., New York. 1940. Price, \$10.00.

The eleventh edition of this well known book is definitely within its usual excellent standards.

This edition, however, is somewhat different from its predecessors in that approximately 35 collaborators with information in specialized pediatric fields have contributed. With these collaborators there has been no loss of uniformity of style nor thoroughness.

The arrangement of the book has not changed in any essential detail. It now contains approximately 1450 pages divided into 21 sections, a new section "Diseases of the Eyes" having been added. "Premature Infants" is now given a separate section, and "Diseases of the Blood" is now grouped under the "Circulatory System."

Revision varying from a very minor to a very marked degree is evident through the entire book. Sections dealing with diseases of the newborn, prematures, nutrition, and many other subjects have undergone drastic changes. Many new topics have been added.

The book cannot be too strongly recommended to students and all others with specialized interest in pediatrics. It contains all the newer concepts of disease and therapy in their most recent form, and is quite different from many textbooks which are old at the time of publication.

W. M. S.

Über die integrative Natur der normalen Harnbildung. In Three Parts. By GÖSTA EKEHORN, Helsingfors. Part I, 616 pages; Part II, 418 pages; Part III, 292 pages; 15 × 24 cm. Mercators Tryckeri, Helsingfors. 1938.

Those who desire a scientific survey of recent work on kidney physiology should avoid these three volumes. They offer an extraordinarily voluminous and tedious argument (1389 pages), very poorly related to recent experimental work, and leading to some erroneous conclusions. The author attempts to discuss all phases of the filtration-reabsorption theory, and is particularly concerned with the forces involved in tubular activity. Unfortunately he gives no experimental evidence of his own, and is unfamiliar with much relevant recent literature. He places great emphasis upon the old paper of Marshall and Kolls (1919) in which the results of kidney denervation were studied and upon the work of Rehberg (1926) in which the U/P ratio of creatinine was first used to calculate plasma clearances in man. The author is apparently unaware that it is now known (Shannon, 1935) that in the human kidney creatinine is in part secreted by the tubules and cannot be used, without correction, to calculate the clearances of other substances. He seems to be only dimly aware of the present use of xylose and inulin in clearance work.

One example of the unscientific character of the author's argument may be given. He accepts Keller's description of positively charged granules embedded in otherwise negatively charged cells of the proximal convoluted tubules. He argues that electrolytes must be reabsorbed in this segment since charged structures of both signs are available simultaneously to attract anions and cations. Glucose, he is driven to conclude, must be here reabsorbed in its enol form (a weak acid), attracted by the positively charged granules. The distal tubules, bearing only negative charges, must, he thinks, be able to absorb only positively charged water and non-electrolytes, like urea. Such naive electrostatic philosophy is directly contradicted by the experimental results of Walker, Hudson, Findley and Richards (1937) who have demonstrated that, in the amphibian kidney at least, the distal tubules are the main site of electrolyte reabsorption and acid-base changes. No references to this paper and other related work are given.

The author needs to learn that the problems of kidney function cannot be resolved by weaving dreams concerning the organ. Here, as always, the only sure approach to understanding is by the experimental road.

W. R. A.

Neurology. By S. A. KINNIER WILSON, M.A., M.D., D.Sc. Edited by A. NINIAN BRUCE, F.R.C.P., D.Sc., M.D., Consulting Physician Bangour Mental Hospital and St. Andrew's Hospital, Stirches. Two volumes, lxvi + 1836 pages, 348 illustrations. Williams & Wilkins Co., Baltimore. Price, \$21.00.

This large two volume work is a comprehensive survey of clinical neurology. Written in the clear pungent style so characteristic of Kinnier Wilson, it is a credit to British neurology. The many hundreds of references in the form of footnotes

show a prodigious amount of work. The manuscript was not completed at the time of the author's unexpected death. However, full particulars were found among his papers regarding the plan of the book. The task of compiling and editing the manuscript and revising and adding to the references was done by A. Ninian Bruce, to whom thanks are due for carrying out a difficult task so well. Anyone who knew Wilson will agree that the forceful style, the use of many new words, and the strong opinions expressed are evidence that the manuscript has not been changed by the editor.

Many chapters are excellent, particularly those which deal with subjects in which the author was especially interested or ones which he considered of paramount importance. These include such subjects as lenticular degeneration, paralysis agitans and other related syndromes, epilepsy and syphilis of the nervous system. Considerable attention is devoted to special forms of toxicosis of the nervous system such as alcoholism, Indian hemp intoxication, carbon monoxide poisoning, etc.

There are several important omissions probably due to lack of completion of the manuscript. There is no discussion of aphasia or apraxia, nor are the syndromes associated with occlusion of important cerebral arteries, such as the anterior and middle cerebrals and the posterior-inferior cerebellar, presented. Despite these omissions, the work is a great one because of its value as a reference work and the many admirable descriptions of disease entities. It should be of great value to anyone interested in the nervous system and should be in the hands of every neurologist and internist.

A. C. G.

Tuberculosis of the Bone and Joint. By G. R. GIRDLESTONE, M.A., B.M. Oxon., F.R.C.S. Eng. 265 pages; 25 × 17 cm. Oxford University Press, New York. 1940. Price, \$8.75.

The present day conception of bone and joint tuberculosis is the result of a gradual evolution of ideas on this subject. Skeletal tuberculosis is now considered one manifestation of a tuberculous infection which has other foci elsewhere in the body. This conception brings this form of the disease into closer connection with the field of work of the internist.

Medical men hence will be particularly interested in the earlier chapters of Mr. Girdlestone's book in which the author discusses these relations of skeletal tuberculosis to tuberculosis in other situations. The sections on the diagnosis of bone and joint tuberculosis will also be of interest. More emphasis could be laid upon the general radiological appearances of a tuberculous joint as compared to other chronic lesions.

The remainder of the book is devoted to the more exclusively orthopedic aspects of tuberculosis of bones and joints. Girdlestone is in accord with many other orthopedic surgeons as to the gloomy prospect of obtaining a useful range of motion and subsidence of the lesion. He, too, favors operative fusion to completely immobilize a joint as the best means today of obtaining a relative cure. On the other hand he gives his end result figures with the conservative or non-operative measures and compares them with those obtained by more radical procedures. Many works on this subject emphasize the one phase and ignore the other, but it can be said of Mr. Girdlestone that he approaches the subject with an open mind and states his results fairly, with the preponderance of evidence favoring the radical cure of tubercular skeletal lesions by operative fusion of the joint.

H. F. U.

COLLEGE NEWS NOTES

PUBLICATION OF THE HISTORY OF THE AMERICAN COLLEGE OF PHYSICIANS

On December 15, 1940, Dr. William Gerry Morgan, Washington, D. C., College Historian, presented to the Board of Regents the completed volume of "The American College of Physicians—Its First Quarter Century," a work on which the Historian had been engaged for the past four years. The History was authorized during the Presidency of Dr. Ernest B. Bradley in 1936, and the preparation of the volume required long and arduous review of the transactions of the College from its initiation in 1915. Dr. Morgan called upon other individuals to assist in the preparation of special chapters on matters with which they were especially familiar, or on which they were especially competent to write. The contents include: "Preface," by Dr. George Morris Piersol, Secretary-General; "The Founding of the College," Dr. William Gerry Morgan; "The Presidents of the College," Dr. William Gerry Morgan; "Other Officers," including The Secretary-Generals, The Treasurers, The Editors of the Journal, The Chairman of the Board of Governors and the Executive Secretary, Dr. William Gerry Morgan; "The Constitution and By-Laws" by Mr. Edward R. Loveland, Executive Secretary; "Financial Record of the College" by Mr. Edward R. Loveland, Executive Secretary; "The Publications of the College" by Dr. Maurice C. Pincoffs, Editor of the ANNALS OF INTERNAL MEDICINE; "The American Board of Internal Medicine" by Dr. Walter L. Bierring, first Chairman of that Board; "My Recollections of the Period," 1925–29, by Dr. Charles F. Martin, former President of the College; "The History of Recent Years" by Dr. James Alex. Miller, former President of the College. Part II of the book is devoted to the chronology of the College, consisting of an abstract from the past Minutes of the College, tracing the actual developments, the formation of policies and the growth and expansion of the organization to the end of the Cleveland Annual Session, 1940. As a concluding chapter, there is a description of the present objectives, activities, administration and requirements of admission.

The book is an example of practical, artistic and good book-making. It is bound in green buckram, stamped in gold with the Corporate Seal of the College. The paper stock represents one of the finest grade of dull coated paper with a complete absence of glare or reflection. The type was selected from a type face and point easily read.

When the publication of the History was first authorized, the Board of Regents directed that it be sent to all Fellows and Masters of the College in good standing. Upon examination of the volume in its completed form, the Board of Regents expressed the desire to give a copy of the History also to all Associates of the College in good standing, and to have a sufficient reserve stock to furnish a copy gratis to every new physician elected to the College during the next three years.

The volume may be purchased by individuals, societies or libraries at the nominal cost of \$2.00, postpaid.

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

Books

- Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn.—“Nelson's Loose-Leaf Specialties in Medical Practice,” Volumes I and II;
- Capt. Harry G. Armstrong (Associate), (MC), U.S.A., Toronto, Can.—“Principles and Practice of Aviation Medicine”;
- Dr. Leon H. Collins, Jr., F.A.C.P., Philadelphia, Pa.—“Internal Medicine in Dental Practice”;
- Dr. D. Sclater Lewis, F.A.C.P., Westmount, Que.—“Pharmacopoeia and Clinical Methods of the Teaching Hospitals, McGill University.”

Reprints

- Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
- Lieut. Col. Joseph R. Darnall, F.A.C.P. (MC), U. S. A., Washington, D. C.—1 reprint;
- Lieut. Col. Daniel B. Faust, F.A.C.P. (MC), U. S. A., Denver, Colo.—2 reprints;
- Dr. Francis R. Finnegan (Associate), St. Louis, Mo.—2 reprints;
- Dr. John Arthur Foley, F.A.C.P., Boston, Mass.—1 reprint;
- Dr. Irvin Reginald Fox (Associate), Eugene, Ore.—1 reprint;
- Dr. Paul John Hanzlik, F.A.C.P., San Francisco, Calif.—25 reprints;
- Dr. Harold Jerome Harris (Associate), Westport, N. Y.—2 reprints;
- Dr. Arthur A. Herold, F.A.C.P., Shreveport, La.—2 reprints;
- Dr. Morrill L. Ilsley, F.A.C.P., Claremont, Calif.—1 reprint;
- Dr. Wesley Wayne Lake (Associate), Pass Christian, Miss.—1 reprint;
- Dr. Benjamin Markowitz (Associate), Bloomington, Ill.—2 reprints;
- Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—2 reprints;
- Dr. Kenneth Phillips, F.A.C.P., Miami, Fla.—2 reprints;
- Dr. Norman Reider, F.A.C.P., Los Angeles, Calif.—1 reprint;
- Dr. Harvey H. Seiple (Associate), Lancaster, Pa.—1 reprint;
- Dr. Isaac J. Silverman, F.A.C.P., Washington, D. C.—3 reprints;
- Dr. Edwin Eugene Ziegler, F.A.C.P., Boston, Mass.—2 reprints.

In addition to the above gifts, acknowledgment is also made of the donation by Dr. William S. Hubbard, F.A.C.P., Philadelphia, Pa., of a copy of “The People's Medical Lighthouse” by Harmon Knox Root, M.D., published in 1856.

REGIONAL MEETING—KENTUCKY A. C. P. MEMBERS

On December 7, 1940, the Kentucky Fellows and Associates of the American College of Physicians held their annual regional meeting at the Good Samaritan Hospital, Lexington, under the Governorship of Dr. Chauncey W. Dowden, with Dr. John Harvey in charge of arrangements. The clinical program consisted of the following presentations:

- “Probable Echinococcus Cyst of the Lung”—Dr. E. J. Murray, Lexington, Ky.
- “Actinomycosis of the Jaw”—Dr. Carl W. Fortune, Lexington, Ky.
- “Two Unusual Cases of Lung Disease”—Dr. Thornton Scott, Lexington, Ky. (by invitation).

Dr. James D. Bruce, President of the College, Ann Arbor, Mich., was to be the guest of honor and give an address on “Fatigue as a Symptom,” but was unable to be present because of illness. Dr. Ernest B. Bradley, who was to conduct a Clinico-Pathological Conference, was also unable to be present because of illness.

In the evening a dinner was held at the Lexington Country Club. Attendance at the meeting was remarkably good, there being forty-three members present. Next year the regional meeting will be held in Louisville.

Among those who spoke at a meeting of the Chicago Society of Internal Medicine on November 25, 1940, were:

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—“Persistence and Recurrence of Toxic Goiter Following Subtotal Thyroidectomy”;

Dr. Raphael Isaacs, F.A.C.P., Ann Arbor, Mich.—“Red Blood Cell Size as an Aid in Diagnosis, Prognosis and Treatment”;

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—“Sulfathiazole in the Treatment of Pneumococcus Pneumonia with a Comparative Study Utilizing Sulfapyridine Therapy” and “Cutaneous and Conjunctival Manifestations of Sulfathiazole Intoxication.”

Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore., spoke on “Chemotherapy of Staphylococcus Infections” at the 10th annual meeting of the American Academy of Pediatrics held in Memphis, Tenn., November 18-20, 1940.

The Southwestern Medical Association held its annual meeting and clinical conference in Tucson, Ariz., November 21-23, 1940, under the presidency of Dr. Orville E. Egbert, F.A.C.P., El Paso, Texas. One of the guest speakers at this meeting was Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y.

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., addressed the Evanston Branch of the Chicago Medical Society, November 7, 1940, on “Recent Studies on Deficiency States and Vitamin Therapy.”

Among the speakers at a special meeting of the New England Heart Association in Boston, Mass., November 8, 1940, to honor the late Dr. Maude E. S. Abbott, formerly Assistant Professor of Medical Research and Curator of the medical museum, McGill University Faculty of Medicine, Montreal, were:

Dr. Charles F. Martin, M.A.C.P., Montreal, Que.—“Dr. Abbott and McGill University”;

Dr. Paul D. White, F.A.C.P., Boston, Mass.—“Her Contribution to Cardiology”;

Dr. Emanuel Libman, F.A.C.P., New York, N. Y.—“Personal Reminiscences.”

On November 19, 1940, Lt. Col. Arthur Parker Hitchens, F.A.C.P., (MC), U.S.A., Philadelphia, Pa., spoke on “History and Biology of the Anthrax Bacillus” and Dr. Henry Field Smyth, F.A.C.P., Philadelphia, Pa., spoke on “Anthrax in the United States” at a symposium on anthrax sponsored by the Bureau of Industrial Hygiene of the Pennsylvania Department of Health and the Philadelphia Department of Health.

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, spoke on “Treatment of Anemia” and Dr. David C. Wilson, F.A.C.P., Charlottesville, Va., spoke on “New Drugs in Neuropsychiatry” at a meeting of the Southwestern Virginia Medical Society in Marion, Va., October 2, 1940.

Dr. George Fordham, F.A.C.P., Powellton, W. Va., spoke on “Developing a Medical Program for a Coal Industry” at a meeting of the Clinch Valley Medical Society held in Norton, Va., October 18, 1940.

The 3rd annual meeting of the American Academy of Dermatology and Syphilology was held in Chicago, Ill., December 8-11, 1940. Among the guest speakers at this meeting were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—“Diseases of the Blood and Blood Forming Organs: Their Relation to the Skin and Mucous Membrane”;

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—“Endocrines and Their Relation to Dermatology.”

Dr. Udo J. Wile, F.A.C.P., Ann Arbor, Mich., conducted a symposium on syphilis at this meeting.

At the annual meeting of the National Foundation for Infantile Paralysis, November 7-8, 1940, held in New York, N. Y., Dr. Herman N. Bundesen, F.A.C.P., Chicago, Ill., was elected Chairman of the Committee on Public Health (Epidemics). Dr. Bundesen succeeds Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, Washington, D. C., who resigned. Dr. James S. McLester, F.A.C.P., Birmingham, Ala., was reelected Chairman of the Committee on Nutritional Research of the Foundation.

The National Institute of Health has formed a new unit for the study of problems of aging, the Unit on Gerontology. This Unit announces that it is conducting a survey of the present trends of active and contemplated investigations in this field. The Unit feels that the analysis of the information elicited by this survey will facilitate closer cooperation among investigators interested in related problems, will emphasize the urgent need for augmented support of studies for the problems of senescence, and will be an invaluable aid in formulating future research programs.

Dr. Edward J. Stieglitz, F.A.C.P., Garrett Park, Md., is in charge of the investigations in gerontology. Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., and Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., are among those who have been appointed to the National Advisory Committee.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., discussed “Functional Gastrointestinal Disorders” at a meeting of the Peoria (Ill.) Medical Society on November 12, 1940.

Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., spoke on “The Control of Tuberculosis” at a meeting of the Fort Wayne Medical Society in Fort Wayne, Ind., October 15, 1940.

Dr. Daniel L. Sexton, F.A.C.P., St. Louis, Mo., spoke on “Endocrine Treatment in General Practice” at a meeting of the Gibson County Medical Society in Princeton, Ind., October 14, 1940.

At a meeting of the Wyandotte County Medical Society in Kansas City, Kan., November 5, 1940, Dr. Henry M. Winans, F.A.C.P., Dallas, Texas, discussed “Anemia—Diagnosis of Difficult Cases.”

At a recent meeting of the section on surgery of the Buffalo (N. Y.) Academy of Medicine, Dr. J. Arnold Bargaen, F.A.C.P., Rochester, Minn., spoke on “Differentiation Between Various Types of Ulcerative Colitis and Their Management.”

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., was the speaker at the autumn postgraduate series of lectures sponsored by the Mahoning County Medical Society in

Youngstown, Ohio, November 14-15, 1940. The subjects of his lectures were: "Present Clinical Status of Chronic Gastritis"; "What Constitutes Adequate Therapy for Chronic Peptic Ulcer"; "Practical Application of Recent Advances in Our Knowledge of Liver Functions"; "Diagnosis and Management of Chronic Ileitis and Ileocolitis"; and "Diagnosis and Management of the 'Irritable Colon.'"

The 9th annual clinical meeting of the Postgraduate Medical Assembly of South Texas was held in Houston, Texas, December 3-5, 1940. Among the guest speakers at this Assembly were the following: Dr. Horton R. Casparis, F.A.C.P., Nashville, Tenn.; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio; Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn.; Dr. Henry K. Mohler, F.A.C.P., Philadelphia, Pa.; and Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa.

Dr. David A. Tucker, Jr., F.A.C.P., Cincinnati, Ohio, spoke on "Daniel Drake, Pioneer Medical Educator of the Middle West" and Dr. Logan Clendening, F.A.C.P., Kansas City, Mo., spoke on "Memorials of Medicine in America" at the fall meeting of the American Association of the History of Medicine, held in Cleveland, Ohio, October 7, 1940.

On November 20, 1940, Dr. Emanuel Libman, F.A.C.P., New York, N. Y., delivered the third annual Louis Gross Memorial Lecture at the Montreal Jewish General Hospital, under the auspices of the Montreal (Can.) Clinical Society. The subject of his lecture was "Endocarditis and 'Libman-Sachs' Disease."

Dr. Francis M. Pottenger, F.A.C.P., Monrovia, Calif., spoke on "Physiologic Approach to Disease" and "The Place of the General Practitioner in the Tuberculosis Program of the Future" at two of the scientific sessions of the Annual Fall Conference of the Oklahoma City Clinical Society held in Oklahoma City, Okla., October 28-31, 1940. Dr. Pottenger was also the principal speaker at the annual banquet of this Society. He spoke on "Can Democracy Be Preserved?"

The 2nd Annual Meeting of the Pennsylvania Psychiatric Society was held in Philadelphia, Pa., October 3, 1940. Among the speakers at this meeting were the following:

Dr. Samuel B. Hadden, F.A.C.P., Philadelphia, Pa.—"Treatment of the Neuroses by Class Technic";

Dr. Lauren H. Smith, F.A.C.P., Philadelphia, Pa.—"First Impressions of Electroshock Treatment in the Psychoses";

Dr. Howard K. Petry (Associate), Harrisburg, Pa.—"Mental Hygiene."

At this meeting Dr. Henry I. Klopp, F.A.C.P., Allentown, Pa., was elected President and Dr. Baldwin L. Keyes, F.A.C.P., Philadelphia, Pa., President-Elect. Dr. William W. Richardson, F.A.C.P., Mercer, Pa., was elected one of the Councillors, and Dr. George J. Wright, F.A.C.P., Pittsburgh, Pa., was elected one of the Auditors.

Dr. Paul H. Ringer, F.A.C.P., Asheville, N. C., was elected President of the Southern Medical Association at its recent meeting in Louisville, Ky.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented an exhibit on "Deficiency Disease with Special Reference to Diagnosis and Treatment" at the Assembly of the Inter-state Post Graduate Medical Association of North America held in Cleveland, Ohio, October 14-18, 1940.

Dr. Kelly also presented a paper on "The Present Status of Deficiency Disease with Special Reference to Vitamin Therapy" before the Burlington County Medical Society at Moorestown, N. J., on November 14, 1940.

Dr. Mark Gerstle, Jr., F.A.C.P., has been assigned to active duty at the U. S. Naval Training Station, San Diego, Calif. Dr. Gerstle holds the rank of Lieutenant in the Medical Corps of the U. S. Naval Reserve.

Dr. Rufus S. Reeves, F.A.C.P., Philadelphia, Pa., was the guest speaker at a meeting of the Hartford (Conn.) Medical Society, November 18, 1940. Dr. Reeves spoke on "Graduate Medical Education."

Dr. Harold J. Harris (Associate), Westport, N. Y., gave a radio address over station WNYC on the subject of brucellosis, under the auspices of the New York Academy of Medicine, December 12, 1940.

On December 16, 1940, the Northern Medical Association of Philadelphia held its regular meeting. Among those who spoke at this meeting were:

Dr. Harold L. Goldburgh, F.A.C.P., Philadelphia, Pa.—"Weil's Disease—Prevalence and Diagnosis";

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—"Story of Ulcer of the Stomach and Duodenum."

Dr. Dan G. Stine, F.A.C.P., Columbia, Mo., was named President-Elect of the Mississippi Valley Medical Society at the recent annual meeting on November 17, 1940, of the Board of Directors. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was reelected Secretary-Treasurer. Among those elected to the Board of Directors of this Society were Dr. E. Sanborn Smith, F.A.C.P., Kirksville, Mo., and Dr. George B. Lake (Associate), Waukegan, Ill.

The 3rd Annual Congress on Industrial Health sponsored by the Council on Industrial Health of the American Medical Association was held in Chicago, Ill., January 13-14, 1941. Dr. Edward J. Stieglitz, F.A.C.P., Bethesda, Md., spoke on "Aging as a Problem of Industrial Health," and Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa., spoke on "The Role of the Physician in Industry in the Control of Acute Respiratory Disease." Dr. Francis E. Seneor, F.A.C.P., Chicago, Ill., presided at a clinic and symposium on "Industrial Dermatoses."

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was elected President of the New Jersey Gastro-enterological Society, a chapter of the National Gastro-enterological Association, at the December meeting of the Society held in Newark, N. J. Among those elected to the Executive Board of this Society were Dr. Manfred Kraemer, F.A.C.P., Newark, N. J., and Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J.

Dr. Lyle Motley, F.A.C.P., Memphis, Tenn., spoke on "Indication and Uses of Sulfanilamide, Sulfapyridine, Sulfathiazole" at the meeting of the Third Councilor District Medical Society in Helena, Ark., October 24, 1940.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., who is Secretary of the Mississippi Valley Medical Society, has announced that the Society offers annually a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay

on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Cedar Rapids, Iowa, October 1-3, 1941, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal*. Contributions shall not exceed 5000 words, be typewritten in English in manuscript form, submitted in five copies and be received not later than May 1, 1941.

Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health, City and County of San Francisco, Calif., has received the following citation from the Consulate General of Mexico: "I have the honor and high personal privilege to inform you that I have been designated by the Secretary of Foreign Affairs of the Government of Mexico to express to you the official recognition by the Mexican Government of your distinguished services in your field, and to convey to you its gratitude and appreciation of your work."

Dr. William M. Ballinger, F.A.C.P., Washington, D. C., has been made Associate Professor of Gastro-enterology at the Georgetown University School of Medicine, Washington, D. C.

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., recently spoke on "Relation of Physiology to Modern Medicine" at a joint meeting of the Des Moines Academy of Medicine and the Polk County Medical Society in Des Moines, Iowa.

Among the speakers at a symposium on chemotherapy presented by the Long Island College of Medicine, New York, N. Y., were the following:

Dr. Yale Kneeland, Jr. (Associate), Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons—"The Sulfonamides in Pneumonia";

Dr. Josephine B. Neal, F.A.C.P., Clinical Professor of Neurology, Columbia University College of Physicians and Surgeons—"The Sulfonamides in Meningitis";

Dr. Elliston Farrell (Associate), Assistant Clinical Professor of Medicine, Long Island College of Medicine—"Toxic Reactions."

Dr. David C. Wilson, F.A.C.P., Charlottesville, Va., was elected President of the Mental Hygiene Society of Virginia at the annual meeting in Richmond, October 31, 1940.

Dr. Lawrence Kolb, F.A.C.P., Washington, D. C., was one of the guest speakers at this meeting. Dr. Kolb discussed treatment and research in the field of mental disease.

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., spoke on "The Present Status of Chemotherapy in the Treatment of Infectious Diseases" at the annual meeting of the Association of Life Insurance Medical Directors in Boston, October 16-18, 1940.

Dr. James K. Hall (Associate), Richmond, Va., was elected Vice President of the Southern Psychiatric Association at its recent annual meeting held in Jacksonville, Fla.

Dr. Henry Mason Smith, F.A.C.P., Tampa, Fla., spoke on "The Psychological and Economic Influence of Alcohol" at this meeting.

At the 19th annual meeting of the Central Neuropsychiatric Association held in Milwaukee, Wis., October 25-26, 1940, Dr. William C. Menninger, F.A.C.P., Topeka, Kan., was reelected Secretary. Dr. Theodore L. Squier, F.A.C.P., Milwaukee, Wis., spoke on "Emotional Factors in Allergic States," Dr. Andrew I. Rosenberger, F.A.C.P., Milwaukee, Wis., spoke on "Observations on Treatment of Amyotrophic Lateral Sclerosis (Leukopoliomyelopathy) with Vitamin E," and Dr. Carroll W. Osgood, F.A.C.P., Wauwatosa, Wis., presented a symposium on shock therapy.

Dr. James J. Waring, F.A.C.P., Denver, Colo., was elected President of the American Clinical and Climatological Association at its annual meeting in White Sulphur Springs, W. Va., October 28-30, 1940. Dr. Benjamin M. Baker, Jr., F.A.C.P., Baltimore, Md., and Dr. Frank A. Evans, F.A.C.P., Pittsburgh, Pa., were elected Vice Presidents of this society.

Among those who spoke at this meeting were the following:

Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Coronary Thrombosis—Ten Years Later";

Dr. Robert L. Levy, F.A.C.P., New York, N. Y.—"Relief of Anginal Pain by Paravertebral Alcohol Block: A Summary of Ten Years' Experience";

Dr. F. Janney Smith, F.A.C.P., Detroit, Mich.—"Kidney Complications of the Chemotherapy of Pneumonia";

Dr. Frederic M. Hanes, F.A.C.P., Durham, N. C.—"The Therapy of Deficiency States."

Dr. Charles W. Mills, F.A.C.P., and Dr. Orin Joicevious Farness (Associate), Tucson, Ariz.—"Coccidioides Immitis Infection in Southern Arizona";

Dr. Truman G. Schnabel, F.A.C.P., and Dr. Ferdinand Fetter, F.A.C.P., Philadelphia, Pa.—"Fever Therapy in Rheumatoid Arthritis."

The Collier Trophy, awarded annually for the greatest achievement in aviation in America and one of the most important national awards in aviation, was recently presented to Captain Harry G. Armstrong (Associate), (MC), U. S. A., and Dr. Walter M. Boothby, F.A.C.P., Rochester, Minn. Presentation of this trophy was made by President Roosevelt on behalf of the National Aeronautic Association and was presented to the physicians for "their contribution to the safety record by their work in the field of aviation medicine generally and pilot fatigue in particular."

Dr. Fred W. Wilkerson, F.A.C.P., Montgomery, Ala., spoke on "Cardiac Neuroses" at a recent meeting of the Northwestern Division of the Medical Association of the State of Alabama held in Reform, Ala.

On November 19, 1940, Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga., gave one of the De Lamar Lectures sponsored by the Johns Hopkins University School of Hygiene and Public Health. The subject of his lecture was "Dietary Problems of the Southern United States."

Dr. August A. Werner, F.A.C.P., St. Louis, Mo., delivered on November 27, 1940, the first Max Ballin Lecture, sponsored by the North End Clinic of Detroit, Mich., on "Recent Advances in Endocrine Therapy." On December 4, 1940, Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., gave the second lecture of this series. Dr.

Alvarez spoke on "Recent Advances in Treatment of Food Allergy." The third lecture was given December 11, 1940, by Dr. Harold J. Jeghers (Associate), Boston, Mass. Dr. Jeghers spoke on "Recent Advances in Vitamin Therapy."

The 37th annual meeting of the Puerto Rico Medical Association was held in Santurce, P. R., December 12-15, 1940, under the presidency of Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R. Among the speakers at this meeting were the following:

Dr. Louis F. Bishop, F.A.C.P., New York, N. Y.—"Coronary Disease—Its Diagnosis and Treatment";

Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill.—"Trends in Specialization in Medicine";

Dr. Ramon M. Suarez, F.A.C.P., and Dr. Enrique Koppisch, F.A.C.P., San Juan, P. R.—"Weil's Disease in Puerto Rico."

Dr. Ralph C. Matson, who is Chairman of the Committee for the Advancement of Scientific Programs in Organized Medicine, of the American College of Chest Physicians, organized and conducted a postgraduate course in diseases of the chest. The course was given under the auspices of the University of Oregon Medical School and the Pacific Northwest section of the American College of Chest Physicians, comprised of Fellows of the College residing in Oregon, Washington, Idaho and Montana. Sixty-seven doctors from this area attended the meeting, which was a two-day session given on December 13 and 14, 1940.

Dr. C. F. De Garis, F.A.C.P., Professor of Anatomy at the University of Oklahoma School of Medicine, has been awarded the A. Cressy Morrison Prize in Natural Science for 1940 by the New York Academy of Sciences for a paper entitled, "The Aortic Arch in Primates." This paper reports the patterns of branches of the aortic arch in a large collection, each family of the Order Primates being represented. The relation of thorax shape to aortic branching is a point of special inquiry. The same type of study, using the same material, will be extended to the heart and lungs.

It is said the strength of this paper rests mainly on the abundant material, most of which was acquired by the author during his stay at the Johns Hopkins University Medical School, 1925-36. The Prize was accompanied by an award of \$200.00.

Western Reserve University has recently announced a grant from Commodore Louis D. Beaumont, formerly of Cleveland, now residing in Florida, of \$8,500.00 to continue the research in hypertension being carried on by Dr. Harry Goldblatt, Professor and Associate Director of the Institute of Pathology and the recipient of the John Phillips Memorial Award by the American College of Physicians in 1938.

NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 15, 1940, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

ELECTIONS TO FELLOWSHIP

December 15, 1940

Fellowship Candidates

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ton, D. C.

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Z. Cason

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Giddings
Joseph Carey Massee, Atlanta C. W. Strickler, Trimble Johnson, Glenville
Giddings
Cyrus Warren Strickler, Jr., Atlanta Russell H. Oppenheimer, J. G. Bachmann, Glen-
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 Willard O. Thompson, A. C. Ivy, James G. Carr, LeRoy H. Sloan
 L. C. Gatewood, James G. Carr, LeRoy H. Sloan
 James G. Carr, Italo F. Volini, LeRoy H. Sloan
 A. C. Ivy, Lowell D. Snorf, LeRoy H. Sloan
 Lowell D. Snorf, James G. Carr, LeRoy H. Sloan

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Elijah Kaplan, John O. Woods, R. R. Snowden

Thomas Arthur Johnson, Drexel Hill

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George B. Lawson, J. W. Preston, Walter B. Martin

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Edwin G. Bannick, Robert F. Foster, C. E. Watts

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Walter E. Vest, Frank J. Holroyd, Albert H. Hoge

PUERTO RICO

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Manuel de la Pila Iglesias, Enrique Koppisch, Ramon M. Suarez

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R. J. Collins, A. B. Waiter, H. A. Farris

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Thomas Alphonsus Lebbetter, Yarmouth

Gerald R. Burns, R. J. Collins, H. A. Farris

Saskatchewan

Harold Sugarman, Saskatoon

D. M. Baltzan, P. H. Sprague, G. F. Strong

"RESOLVED, that the following list of 19 be and herewith are elected to Fellowship in the American College of Physicians as of April 20, 1941:"

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James M. Faulkner, Elliott P. Joslin, William B. Breed

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OBITUARY

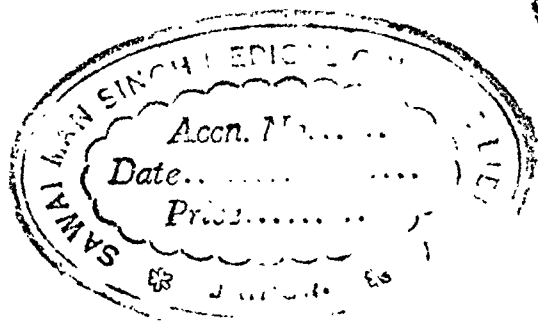
DR. FREDERICK J. COX

Dr. Frederick J. Cox, F.A.C.P., of Gilbertsville, N. Y., died on December 5, 1940, at the Flower Hospital in New York City. Dr. Cox was born in Albany, N. Y., June 28, 1866. He received his A.B. degree from Williams College in 1889 and graduated from the Albany Medical College in 1892. From 1895 to 1912, he was visiting physician to the Homeopathic Hospital of Albany, and in 1912 became the chief of the medical service of this hospital. During the World War, Dr. Cox served as Assistant Chief of the Medical Service, Base Hospital, Camp Upton, L. I., N. Y., and he attained the rank of Major in the Medical Corps of the U. S. Army. In his earlier career, he pursued postgraduate training at the École de Medicine in Paris, France, and later at the Harvard Medical School, Boston. He was a member of the American Institute of Homeopathy, the Homeopathic Medical Society of the State of New York, the Albany County Medical Society and the American Medical Association. He was a member of the American Congress on Internal Medicine and in 1923 was elected to Fellowship in the American College of Physicians.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

ERRATUM

On page 1121 of the December, 1940, issue of the ANNALS Postgraduate Course No. 6, Gastro-Enterology, appeared on the dates "April 7-12, 1941." The dates should have been April 14-19, 1941.



ANNALS OF INTERNAL MEDICINE

VOLUME 14

FEBRUARY, 1941

NUMBER 8

NEUROLOGICAL SYMPTOMS AND CLINICAL FINDINGS IN PATIENTS WITH CERVICAL DEGENERATIVE ARTHRITIS *

By STACY R. METTIER, M.D., F.A.C.P., and CHARLES S. CAPP, M.D.,
San Francisco, California

THE occurrence of pain and muscular stiffness about the neck and in the shoulder-girdle, and the radiation of pain down the arm or into the precordial region, has been the subject of considerable discussion in recent years. These symptoms may be readily explained when they are induced by a definite etiologic factor such as traumatic injury to the brachial plexus or pressure of cervical rib on this structure, bursitis, or the destruction of cervical vertebrae by bacterial or neoplastic processes. However, there are instances of pain which are not so easily explained and in which the origin is doubtful. In the medical literature one finds such conditions designated as radiculitis, pain of nerve-root origin, neuritis, or the "radicular syndrome" as described by Gunther and Kerr.¹

Many years ago some of these symptoms were described by von Bechterew,² Strümpell,³ Marie,⁴ Bailey and Casamajor⁵ and others, which they attributed to arthritic changes in the vertebral column. These authors, however, noted that there was no direct relationship between the amount of arthritic change and the degree of the neurologic manifestations.

In 1936, Hanflig⁶ reported a group of 30 cases of radiculitis in which rigidity of the neck, pain, and other sensory and sometimes motor disturbances were the outstanding symptoms. In these cases, there was no evidence of local disease of the arm and shoulder, and he believed the pain was probably a manifestation of irritation or actual inflammation of cervical spinal nerve-roots due to cervical arthritis. He stated that the roentgenograms may or may not show evidence of hypertrophic changes.

In the same year, Turner and Oppenheimer⁷ reported the results of their

* Read before the American Rheumatism Association at the Fifth Annual Meeting, San Francisco, June 13, 1938. Received for publication September 7, 1939.

From the Departments of Medicine and Roentgenology, University of California Medical School.

Assisted by a grant from the Christine Breon Fund for Medical Research.

studies of the cervical spine in 50 patients with symptoms similar to those noted by Hanflig. They observed narrowing of the intervertebral discs which they held responsible for the symptoms whether hypertrophic arthritis was present or not.

Morton⁸ reported three cases which showed the presence of hypertrophic spurs on the posterior aspects of the cervical vertebrae. These spurs, it was stated, projected into the spinal canal and caused pressure on the cord or encroachment on the cervical foramina, giving rise to symptoms.

In carrying out their studies, Turner and Oppenheimer and Morton used a special roentgenographic technic in which the posterior aspects of the vertebrae and the vertebral foramina were rendered visible by taking oblique projections of the spine.

The present study was undertaken to analyze the symptoms suggestive of cervical nerve-root origin occurring in patients presumably having osteoarthritis, and to attempt to correlate these symptoms with roentgenograms of the cervical vertebrae taken in the antero-posterior, lateral and oblique projections.

During the past few months, we have examined 30 patients with symptoms characteristic of cervical radiculitis. Most of the patients in this group were between 40 and 60 years of age. Three were under 40 years of age.

The symptoms complained of most frequently were pain, rigidity of the neck, and muscular weakness of the hand or arm. The onset of pain was usually abrupt and in many cases was first noticed by the patient on awakening in the morning. More often than not the pain was localized in and about the shoulder, especially about the insertion of the deltoid muscle, or radiated down the arm into the fingers. As a rule, these symptoms appeared months or even years before there were any complaints of neck discomfort. Usually the pain was unilateral but, with the exception of a few instances, it became bilateral at some time during the progression of the pathologic condition. The pain varied from one of an excruciating character to a dull, aching sensation. At times it was described as sharp, jabbing, needlelike and penetrating; at other times as a prickly or stinging feeling. Some patients complained only of numbness and tingling in the fingers or of a drawing or dead, aching sensation in the muscles of the arms.

The loss of freedom of use of one upper extremity was a common complaint. Many patients had become unable to comb their hair or to extend the arm behind the back to adjust their clothing. Others were unable to perform fine movements such as sewing or writing, and some of them found it difficult to grasp objects.

A few patients became conscious of pain in the neck during the early course of illness, but in most patients it was a late development. In no instance was there definite restriction of movement of the head and neck, but it was often stated that pain in the neck was induced by jarring of the body. The discomfort was sometimes described as a "headache at the base

of the brain," as a feeling of "congestion" at the base of the brain, or simply as muscular soreness.

In none of the patients examined was there evidence of atrophy of the muscles of the hands, arms or shoulder-girdle. In all instances the reflexes of the arm showed normal reactions.

Although the symptoms in these patients varied in degree, in their general character and distribution they were uniform enough to lead one to suspect the presence of a common underlying pathologic process. Such, however, was not the case in our experience, and therefore we are not in entire agreement with Turner and Oppenheimer who state, "If neurological symptoms existed in the patient and directed us toward examination of the cervical spine, there was a consistent finding of a narrowing of one or more of the intervertebral spaces regardless of whether we were dealing, in addition, with hypertrophic arthritis, infectious arthritis, or with traumatic displacement."

The demonstration of the presence or absence of arthritis in the cervical vertebrae in our 30 patients was determined by the roentgenographic findings. Accordingly, synovial swelling or inflammatory reaction in the soft tissue of the joints indicative of early changes was precluded by this method of examination. The cases were divided into three groups, depending upon the amount of alteration noted. In 18 patients, marked hypertrophic changes were observed. These consisted of circumferential osteophyte formation which projected into the intervertebral canals from the superior or inferior margins of the vertebrae, and caused from slight to marked narrowing of the foramina, depending on the size of the hypertrophic spurs. The osteoarthroses occurred more frequently on the left side than on the right. In addition, in the regions of exostoses, the intervertebral discs were thinned out, so that there was from slight narrowing to almost complete obliteration of the intervertebral spaces. The disc cartilage adjacent to small processes was not necessarily thinned out. It was noted with interest that the sites of predilection were between the fifth and sixth and the sixth and seventh vertebrae.

The symptoms elicited from the seven patients segregated in the second group were similar to those described above, but the roentgenographic findings of osteoarthroses were considered minimal in degree. In these seven patients, there was a minimal to slight degree of osteophyte formation on the adjacent surfaces of the vertebrae, usually the fifth and sixth. This small amount of arthritis was accompanied by narrowing of the intervertebral discs in only three patients. In most of the patients, there was some sclerosis of the articular facets.

In four patients with symptoms of radiculitis, there was no apparent abnormality of the articular facets in the roentgenograms, no evidence of proliferative new bone formation at the margins of the vertebrae, no noticeable narrowing of the intervertebral foramina or thinning of the intervertebral discs.

CASE REPORTS

Case 1. D. D. DeL., a white American female 57 years of age, complained of pain in the shoulders and neck and weakness of both hands. She stated that six months prior to coming to the Out-Patient Department, she awakened one morning with a feeling that the left arm was dead and was conscious of numbness and tingling across the back of the thumb, index and middle fingers. During the course of the morning, the symptoms subsided, but subsequently were of daily occurrence. She found that lying on the left side increased her discomfort. About a week after the onset of her illness, similar symptoms appeared in the right arm and hand. Four weeks later she noticed some difficulty in grasping objects, particularly in attempting to use the curling-iron which, on occasions, actually fell from her hand. About two or three months ago she first noticed sharp, stabbing pains in both wrists which she stated "felt as though needles were being pushed through." At this time she noticed

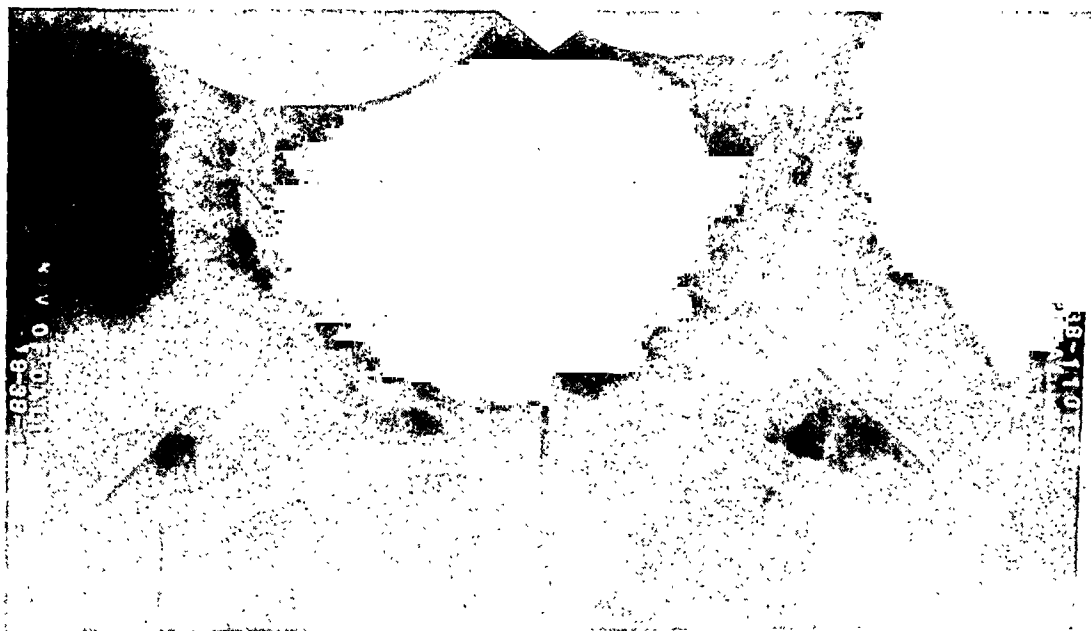


FIG. 1. *Case 1.* Shows narrowing of joint spaces between fifth and sixth, and sixth and seventh cervical vertebrae. Films were made from the oblique projection.

stiffness of the neck on awakening in the morning and "a sore feeling deep in the back of the neck." This soreness spread into the left shoulder. Her symptoms were aggravated by turning the neck, were alleviated by warmth and, as a rule, gradually subsided during the course of the day. At no time had there been an inability to raise her arms above the level of the shoulders.

Physical examination revealed no abnormalities of the reflexes of the upper extremities, and there was no evident atrophy of the muscles of the shoulder-girdle or hands. There was no swelling of the small joints of the hands. As the patient sat in the chair, she rubbed her hands constantly.

The roentgen findings revealed the following: "There is almost total obliteration of the intervertebral joint between the sixth and seventh cervical vertebrae. There is extreme narrowing of the intervertebral canal space by proliferative bone at the margins, more so on the left than on the right side. There is some narrowing of the intervertebral joint between the fifth and sixth vertebrae also. There is no evidence of cervical ribs nor of metastases nor of fracture or dislocation."

Case 2. E. P., a white female aged 45 years, complained of pain in the right shoulder and numbness and tingling in the fingers. She stated that for more than 10 years she had had pain recurring at frequent intervals in the right shoulder in the region of the insertion of the deltoid muscle. This was described as an aching sensation similar to a "toothache." This discomfort frequently awakened her about three o'clock in the morning and she learned that some relief could be obtained by the application of heat or by wearing a woolen sweater. About five years ago she became aware of numbness and tingling in the fingers of the left hand. Associated with the onset of this symptom, she noted a transient blanching of the fingers of both hands, followed by a short period when they appeared deep red in color. This phenomenon had occurred off and on since, and was noticed to appear more frequently during the winter months. For the past few months there had been pain and muscle stiffness in the left side of the neck, with radiation into the shoulder.

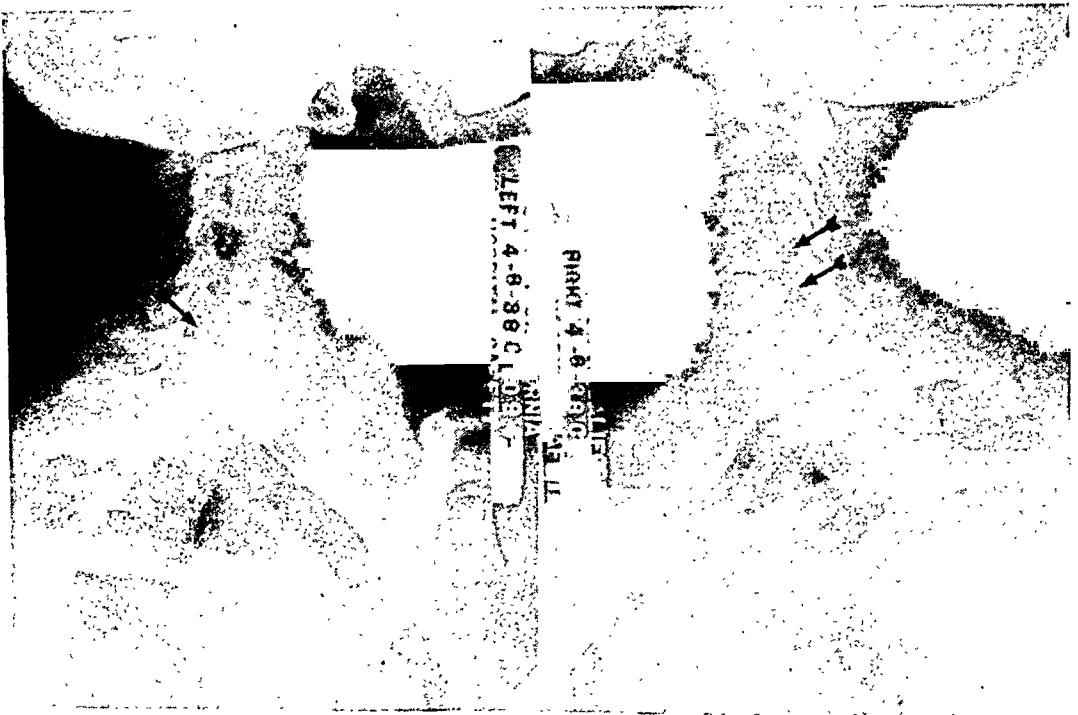


FIG. 2. *Case 2.* An oblique projection showing narrowing of the fifth and sixth, and sixth and seventh intervertebral discs. Note the encroachment on the intervertebral foramen by spur formation.

Physical examination revealed the patient to be slightly overweight. There were no other findings of significance.

Examination of the roentgen films was reported as follows: "The intervertebral discs between cervical 5 and 6 and 6 and 7 are narrowed. There is bony proliferative change encircling the margins of the discs particularly on the lateral side of the posterior edges so that there is encroachment by the spur formations on the intervertebral foramen, particularly the sixth foramen on the left side and the seventh foramen on the right side. There is a left lateral scoliosis involving the lower three cervical vertebrae and the upper five thoracic vertebrae. The greatest convexity is toward the left, being at the level of thoracic 4. There is no evidence of cervical ribs."

The following case is reported as an example of the radicular syndrome with roentgen findings of a minimal amount of arthritis.

Case 3. C. B., a white American female, aged 57 years, complained of pain in the right shoulder. For the past five years, the patient had had recurring pain in the region of the right deltoid muscle. This was described as a sharp, stabbing pain and was accompanied by a constant dull, aching feeling. Soon after the onset of symptoms she found it difficult to put her hand behind her back to tie her apron-strings or to elevate her arm to comb her hair. In addition, there were numbness and tingling of the finger-tips which extended up into the wrist. She was frequently awakened about 3 or 4 o'clock in the morning by these symptoms, especially when she slept on the right side of the body. About three months ago, similar symptoms appeared in the left arm and hand. About one month ago she began having a tired, aching pain between the shoulder-blades which radiated into both shoulders. All of her symptoms were most marked on awakening in the morning, but she found that she could obtain some relief on applying heat at the back of the neck, rubbing her arms with hot water or moderately exercising the muscles of the neck.

The physical examination revealed nothing of significance excepting moderate hyperesthesia of the skin of the hands.

Roentgenographic examination showed the following: "there is no noticeable narrowing of the intervertebral discs. There is only a very minimal degree of marginal osteophyte formation on the superior and inferior edges of the fifth cervical vertebrae. There is no sclerosis of the articular facets."

The following case history is reported as an example of the radicular syndrome but without roentgenographic evidence of cervical osteoarthritis:

Case 4. I. M. C., a white American female, formerly a housewife and now employed as a waitress, complained of pain in the left side of the neck. This pain was described as an aching sensation accompanied by muscle soreness which extended from the base of the neck into the occipital region and radiated out into the left shoulder. These symptoms were first noted about three years ago, and soon after their appearance there were numbness and tingling in the thumb and index finger of the left hand. On occasions there had been blanching of the fingers followed by reddish discoloration. More recently, there had been a drawing sensation in both sides of the neck. Relief is obtained by taking a hot bath or with moderate exercise. Jarring will aggravate the symptoms.

On physical examination, the patient appeared slightly underweight. There were no abnormalities of the reflexes of the upper extremities, but there was definite spasm of the left trapezius muscle. There was no evident swelling of the small joints of the hand, no focal tenderness over the bursa of the shoulder, and the symptoms of the scalenus anticus syndrome were not induced by rotation of the head to the affected side or by pressing down on the shoulder.

Roentgen-ray: "There is no evidence of any abnormality from a bony standpoint, nor evidence of cervical rib. The intervertebral foramina are not narrowed, and there is no evidence of proliferative bony changes at the joint margins."

DISCUSSION

The first two case histories reported here were selected from a group of 17 patients having similar symptoms presumably of nerve-root origin. In these patients there was definite evidence of degenerative arthritis of the cervical vertebrae. The roentgenograms taken in the oblique projection

showed narrowing of the intervertebral foramina by the ingrowth of the marginal osteophytes. The decrease in vertical diameter of the foramina was furthered in many instances by close approximation of the vertebral bodies due to thinning of the intervertebral discs. It is evident from this study that the combination of these two processes may impinge upon the nerve trunk as it passes through the involved foramina or may affect the sympathetic fibers controlling blood flow.

One wonders, however, why this process is able to pick out the sensory fibers in such a high percentage of cases, and not involve the motor fibers at the same time. A possible explanation for this is the fact that the motor fibers of the anterior cervical roots are fewer in number and comprise a bundle only one-third the size of the posterior sensory fibers.⁹ This leads us to the conclusion that actual diminution in the size of the nerve trunk may be sufficient to give rise to the irritative phenomena recognized clinically as the radicular syndrome.

It seems unlikely that a similar process can adequately explain the neurologic symptoms arising in the patients of the second and third groups. In our roentgenograms there was no radio-opaque material present in the intervertebral foramina to suggest impingement upon a nerve bundle. Nathan⁸ in 1916 induced experimental non-suppurative arthritis in animals and noted thickening of the periosteum of the vertebrae. From his studies he concluded that these changes could lead to irritation and compression of nerve roots. Whether or not the sequence of events in man may consist of a preliminary swelling in the periosteum of the cervical vertebrae similar to that produced in the experimental animal, and finally in the formation of new bone, is a matter of speculation. It is hoped that further studies on this problem may be carried out in conjunction with members of the Department of Anatomy.

Viewing the subject from the standpoint expressed by Turner and Oppenheimer that narrowing of the intervertebral spaces was a common lesion in their patients, we were unable to arrive at identical conclusions. We do not doubt the results these authors obtained but do disagree with the statement that narrowing of the intervertebral discs may be a consistent finding, or may be the first change of importance before the development of hypertrophic arthritis.

It is important to emphasize that this syndrome is of relatively frequent occurrence and, as a rule, inadequately treated. This group of 30 patients was seen by us during a period of less than three months. Many of the patients had wandered from one clinic to another in an endeavor to get relief from their symptoms. Many had resorted to forms of treatment not regularly recognized by the medical profession. It was of interest to learn that those who had received a special form of treatment that was basically manipulative in nature had definite relief from their discomfort.

In our clinic, treatment has consisted of heat to the neck, massage, manual

traction and manipulation. The majority of patients are relieved of pain on this regime.

SUMMARY

This syndrome of pain and muscular stiffness about the neck and in the shoulder-girdle, or the radiation of pain down the arm, is of relatively frequent occurrence in persons beyond 40 years of age. From our studies it was learned that in approximately two-thirds of the patients there was roentgenologic evidence of hypertrophic arthritis. In the remaining patients there was no evidence of arthritis or of any other pathologic process in the roentgen-ray films. The value of taking roentgen-ray films in the oblique projection is emphasized. The patients were greatly relieved of their symptoms by the application of heat, massage, manual traction and manipulation, and posture training.

REFERENCES

1. GUNTHER, L., and KERR, W. J.: The radicular syndrome in hypertrophic osteo-arthritis of the spine, *Arch. Int. Med.*, 1929, xliii, 212.
2. VON BECHTEREW, W.: Steifigkeit der Wirbelsäule und ihre Verkrümmung als besondere Erkrankungsform, *Neurol. Centralbl.*, 1893, xii, 426.
3. STRÜMPPELL, A.: Bemerkung über die chronische ankylosierende Entzündung der Wirbelsäule und der Hüftgelenke, *Deutsch. Ztschr. f. Nervenhe.*, 1897, xi, 338.
4. MARIE, PIERRE: Sur la spondylose rhizomélitique, *Rev. de Méd.*, 1898, xviii, 285.
5. BAILEY, P., and CASAMAJOR, L.: Osteoarthritis of the spine as a cause of compression of the spinal cord and its roots, *Jr. Nerv. and Ment. Dis.*, 1911, xxxviii, 588.
6. HANFLIG, S. S.: Pain in the shoulder girdle, arm and precordium due to cervical arthritis, *Jr. Am. Med. Assoc.*, 1936, cvi, 523.
7. TURNER, E. L., and OPPENHEIMER, A.: A common lesion of the cervical spine responsible for segmental neuritis, *ANN. INT. MED.*, 1936, x, 427.
8. NATHAN, W. P.: The neurological condition associated with polyarthritis and spondylitis, *Am. Jr. Med. Sci.*, 1916, clii, 667.
9. LEWIS, W. H.: *Gray's anatomy*, ed. 21, 1924, Lea and Febiger, Philadelphia, p. 23.

STUDIES IN THE CELLULAR EXUDATES OF BOWEL DISCHARGES. III. THE DIAGNOSTIC SIGNIFICANCE OF CELLULAR EXUDATE STUDIES IN CHRONIC BOWEL DISORDERS *

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THE purpose of this paper is to give the practical applications of the findings of a series of studies of the cellular exudates of bowel discharges.

The microscopic examination of bowel discharges for the presence or absence of cells affords the general practitioner a very simple, yet most effective method of determining whether or not there are pathological changes in the bowel wall. The presence of cells in the bowel discharges indicates that pathological changes are taking place. This knowledge is of particular value when following the progress of an inflammatory lesion. The decrease of cells found in the bowel discharges shows that healing is taking place. Thus when cells cease to appear in the bowel discharge, the physician will know that an active pathological condition no longer exists.

The information obtained from cellular exudate studies makes it possible for the practitioner to determine whether a diarrheal condition is related to a breakdown in the bowel wall, such as occurs in chronic ulcerative colitis, or whether it is functional and nervous in origin. When patients with diarrhea are not suffering from pathological change in the bowel wall, cells will be absent from their bowel discharges. This will be true even if the patient is given a saline cathartic, an enema or a colonic irrigation.

MATERIALS AND METHODS

Three types of specimen are generally examined for cellular exudates. These are (1) the normal fecal movement, from which the outside of the mass should be selected because it comes into closer contact with the mucosa and may therefore contain the cellular exudate; (2) the watery discharge which follows a saline cathartic. This is one of the most valuable types of specimen that can be obtained for examination. The patient is given the same preparation for this examination as for the diagnostic study of the stools for chronic amebic dysentery. A dose of epsom salts or of some other saline cathartic should be given, and the patient should be instructed to come to the physician's office to evacuate the bowels. He should discard the major portion of the watery evacuation, but should collect the last of the movement

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that is forced out. This type of specimen is particularly valuable because it may contain cells from pathological areas higher up in the bowel which would be missed if the normal fecal movement only were examined. And finally (3) the terminal mucus evacuated following three normal saline enemas should be collected for microscopic examination. This is by far the most valuable type of specimen to obtain for cellular exudate study because the gross fecal matter is washed away with the first two saline enemas, while mucus only is evacuated after the third. The patient should be instructed to take three enemas, which should follow each other without delay; but he should be warned not to insert the enema tip more than about one or two inches within the sphincter. Otherwise he might cause injury to the bowel wall. The new sigmoid cannula described by Bercovitz¹ can be used to aspirate the terminal mucus in cases where the patient is to have a sigmoidoscopy.

A small amount of the bowel discharge should be emulsified on a glass slide in a drop of Loeffler's methylene blue and should be covered with a coverslip. The cells will take up the methylene blue in this type of preparation so that the cytoplasm will appear as a delicate pale blue while the nuclei will stand out as either solid or ringed bodies within the cell structure. When making the wet coverslip preparation with methylene blue, it is important to make sure that the preparation is carefully emulsified with the dye, and when the coverslip is placed on this emulsion to make sure that it is thin enough so that large black print can be seen through it.

If it is desired to make a permanent preparation, the bowel discharge should be smeared onto a clean glass slide and should then be immersed immediately in warm Schaudinn's fluid. From this point onwards, the staining technic is that which is ordinarily used for making the permanent saline preparations for intestinal protozoa. (Details given by Bercovitz.²)

When specimens have been fixed in formalin and embedded in paraffin, the appearance of the cells will differ from when the specimens have been prepared with the methylene blue or with Schaudinn's solution and stained with Heidenhain's iron hematoxylin technic. A certain amount of shrinkage takes place with the paraffin technic which causes the cells to appear smaller and quite compact, while as a rule the nuclei appear to be solid. This appearance is due to the fact that the hematoxylin stain is taken up as a solid mass. With the wet methylene blue coverslip preparations as well as with the permanent preparations made with Heidenhain's iron hematoxylin technic, the cells retain their natural size and shape so that it is possible to make careful detail studies of the cytoplasm and the nuclei in order to determine what changes may be taking place within the structure of the cell.

CYTOLOGY OF EXUDATES

When specimens are prepared according to the technic outlined, four main types of cell may be found in the bowel discharge upon microscopic examination. Some of these cells are frequently confused with the protozoa of dysentery, but should be clearly differentiated from them.

Epithelial cells generally assume irregular shapes, although they may be oval to round or square. They are sharply defined and can be distinguished readily from the rest of the cellular exudate. The cytoplasm, which is easily seen, is usually quite smooth or finely granular, but it may also contain coarse granules which stain dark. The nuclei of epithelial cells usually appear as open rings and seem to be composed of nuclear membrane, which may be delicate or coarse, on the inner surface of which there either may or may not be beading with granules of different sizes. It is not uncommon to find heavy granules within these open-ringed nuclei. As a rule the centrosome may also be distinguished readily, while upon occasion very delicate lines of chromatin matter may be observed which seem to extend from the centrosome to the nuclear membrane. Since many forms of epithelial cells have been mistaken for amebae, it is necessary to distinguish between them very carefully. (Figure 1.)

Polymorphonuclear leukocytes usually constitute the majority of the cells found in a cellular exudate specimen. However, they assume an entirely different appearance from the polymorphonuclear leukocytes which may be seen in a blood film stained with Wright's or Leishman's modification of the Romanowsky stain. The nuclei, in either the segmented or the young forms, most commonly appear as heavy rings within the cytoplasm of the cell. At times these rings are lined with coarse chromatin beads and a centrosome may be visible. If the fine adjustment of the microscope is focused up and down carefully, it will be possible to observe these rings at different levels within the cell proper. Usually there are three such rings, and with a little experience they can be differentiated from the cysts of protozoa, with which they are most frequently confused. The differential diagnosis will be given when the protozoa which cause dysentery are described.

Polymorphonuclear leukocytes are readily seen in saline smears of the bowel discharge, even when no stain is used. In some cases when the methylene blue stain is used, it will be found that the nuclei of the polymorphonuclear leukocytes absorb the stain. They then appear as solid masses, and present the more commonly recognized picture of this cell. At the present time it is not known exactly what conditions favor the different appearances of the polymorphonuclear leukocytes. In a few instances, some eosinophiles have been observed when wet preparations with Wright's stain have been used. Further work on eosinophiles in the bowel discharges is now in progress (and will supplement this study as soon as it is completed).

Round cells belonging to the lymphocytic series are frequently seen. These cells are usually much smaller than the polymorphonuclear leukocytes. In shape they are round to oval, and have a nucleus which may be either ringed or solid and which takes up the greater part of the cell.

Macrophage cells of endothelial origin are quite commonly seen, especially in cases of bacillary dysentery. In the fresh unstained preparation, these cells are the most striking in the whole field. They are large and

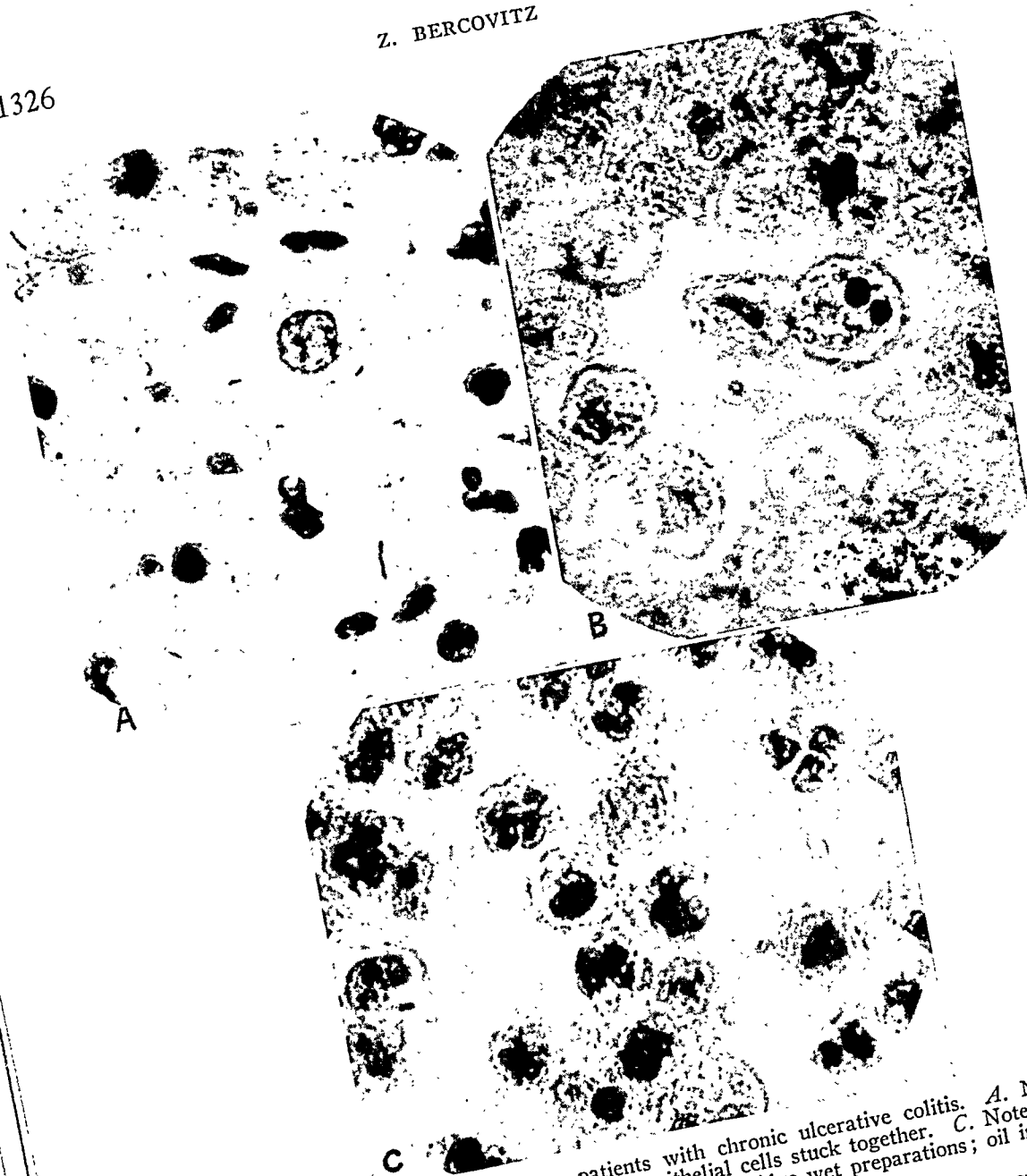


FIG. 1. Cellular exudates from patients with chronic ulcerative colitis. A. Note epithelial cell with ring nucleus. B. Note two epithelial cells stuck together. C. Note different types of polymorphonuclear cells. Loeffler's methylene blue wet preparations; oil immersion.

prominent, with well-defined ectoplasm and nucleus. At times the cytoplasm is vacuolated and may contain ingested particles such as yeast cells, bacteria, or even red blood cells. These cells may develop to an enormous size and some of them have measured more than 100 microns.

THE DIFFERENTIAL DIAGNOSIS OF AMEBIC AND BACILLARY DYSENTERY

Through the brilliant work of Manson-Bahr and his collaborators, as well as of Wenyon and O'Connor, a clear differentiation has been established

between the stools in amebic and in bacillary dysentery. Within the space of a few years, the differences in the stools in these two types of dysentery, which these men had pointed out, were amply demonstrated by men such as Graham, Willmore, Shearman and Anderson, whose work covered the fields of bacteriology, cytology and pathology.

In amebic dysentery, the bowel discharge consists mainly of mucus, which at times is streaked with blood. This discharge has the appearance of a clear, glairy substance, much like the white of an egg. It is generally quite copious in amount, flows freely in the bed-pan, and is difficult to pick up with an applicator. As a rule, it contains a scanty cellular exudate. Evidence may be found of proteolytic digestion of the cells, beginning at the periphery and affecting the nucleus last of all. Clearly defined bodies, about 20 microns in diameter, may be observed scattered among the mucus. If these bodies are watched closely, even under the low power objective, such characteristics as definite changes in shape and progressive motility will be noticed. If the fresh, unstained preparation is examined with the high dry objective or the oil immersion, it will be observed that there is pseudopodia formation with clear differentiation between the ectoplasm and the endoplasm. The nucleus, however, cannot be visualized. This fact constitutes one of the most important differential characteristics of the freshly passed *Endameba histolytica*.

Bacillary dysentery bowel discharge is characterized by a heavy cellular exudate. Cells of all kinds will be found. Polymorphonuclear leukocytes will predominate, but there will also be a few red blood cells, lymphocytes, epithelial cells, plasma cells and endothelial macrophages. It is important to recognize the endothelial macrophages because they seem to resemble free-resting amebae, and are consequently confused with them. These cells are larger than the polymorphonuclear leukocytes and are the macrophages of endothelial origin which were described by Manson-Bahr and his associates. There is usually some vacuolization in these cells, and in the fresh, unstained preparation the nucleus stands out prominently as a heavy ring with beading. It should be observed, however, that the macrophages of endothelial origin have no progressive motility, and any motion that may be seen will be of a pulsating type.

On the basis of these findings, it will be possible to make a provisional differential diagnosis of amebic and bacillary dysentery.

CELLULAR EXUDATE STUDIES AND FINDINGS

During the past four years extensive observations have been made of patients who were free from gastrointestinal disorders and also of patients who had definite bowel complaints in order to determine, if possible, the diagnostic significance of the absence or presence of cellular exudates in bowel discharges.

The initial investigations of this study were concerned with the problem

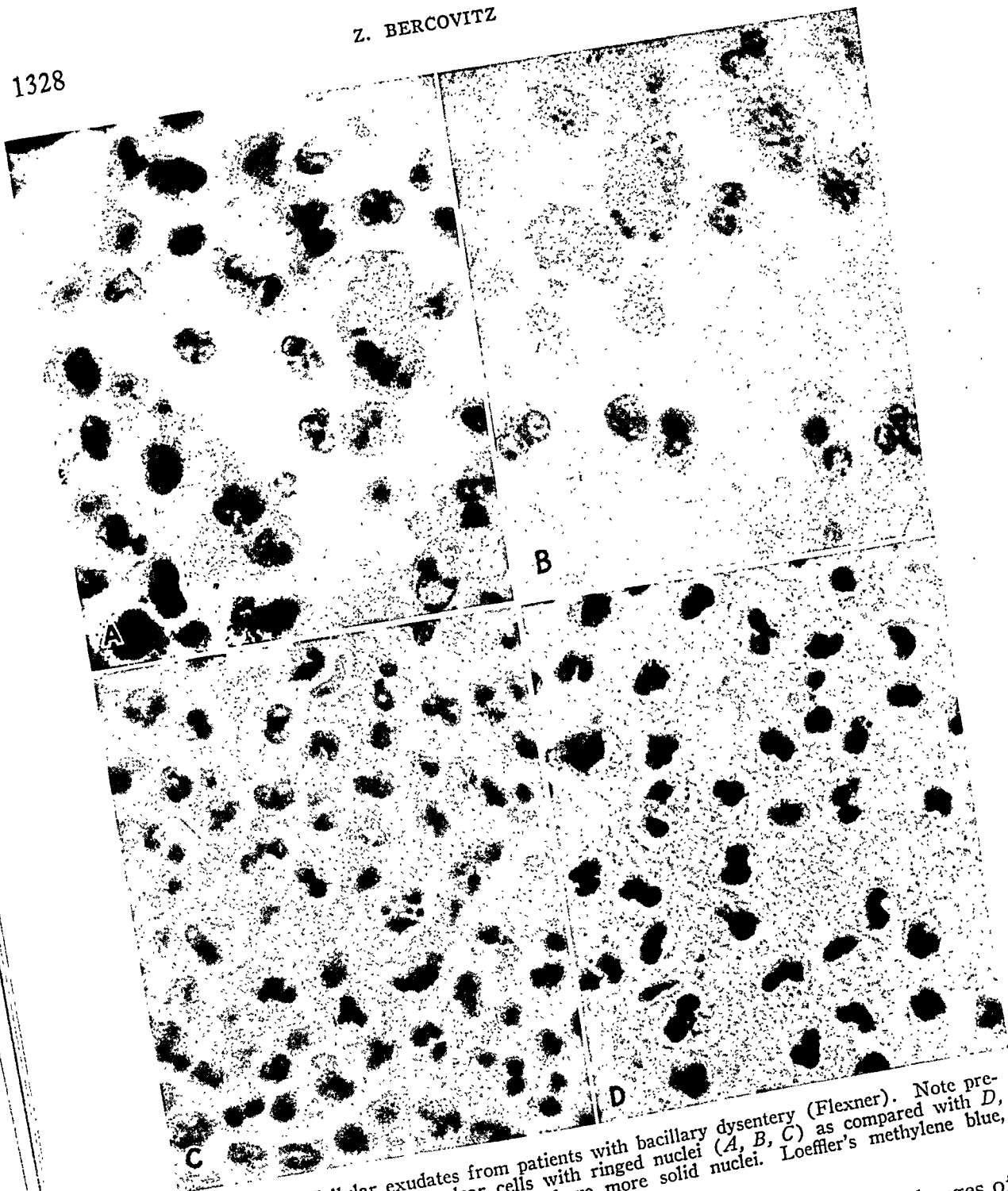


FIG. 2. Cellular exudates from patients with bacillary dysentery (Flexner). Note predominance of polymorphonuclear cells with ringed nuclei (A, B, C) as compared with D, in which the polymorphonuclear cells have more solid nuclei. Loeffler's methylene blue, wet preparations; oil immersion.

as to whether or not cellular exudates should be expected in the discharges of the normal bowel mucosa. Control observations were made of 1123 patients who stated that they had no disorders which could be referred to the

gastrointestinal tract. Altogether 2158 specimens were examined from these so-called normal patients and, with the exception of 11 specimens, all were negative for cells. The 11 positive specimens came from two patients, 57 and 62 years of age, who unfortunately could not be traced for subsequent study. Of the 2158 specimens, 198 were diarrheal movements following dosage with epsom salts.

In order to see whether negative findings would be true whenever pathological change was not present in the bowel mucosa, specimens were obtained at the autopsies of seven individuals. These specimens were taken from several different levels in the gastrointestinal tract, and at the same time scrapings were obtained from the bowel wall at the same locations. Cells of the same type were found in the specimens and in the scrapings, but as they were not the type of cell ever found in the bowel discharges of living persons, it was presumed that they were the result of postmortem degeneration. To check this conclusion, three dogs were given lethal doses of sodium amytal, and their abdomens were opened as soon as respiration ceased. Specimens of the bowel contents from three locations in the colon and also from the terminal ileum were taken for examination, and were found to be negative for cells.

With uniformly negative results for normal bowel mucosa, it was possible to assert that when cells were absent from the bowel discharges, no pathological condition would be found to exist in the bowel mucosa. But in order to discover the relationship of cellular exudates in bowel discharges to pathological conditions in the bowel mucosa, a careful study was made by Bercovitz and Fuller³ of 216 patients who were suffering from various types of bowel complaint.

Of the 216 patients studied, it was found that 66.2 per cent had positive cellular exudates. An analysis of the most important symptoms associated with the various types of bowel complaint found in these patients shows that with pus the positive cellular exudate was 100 per cent; with blood in the stools, 86.9 per cent; with diarrhea, 84.2 per cent; with tenesmus, 83.3 per cent; with alternating diarrhea and constipation, 73.9 per cent; with mucus in the stools, 68.8 per cent; and with constipation, 50 per cent. As these symptoms, with their high percentages for cellular exudates, are associated with definite and progressive pathological conditions which can be identified by sigmoidoscopic and, if necessary, roentgen-ray examinations, it is clear that the cellular exudate study should be made a routine procedure whenever a patient with a bowel complaint reports the presence of any of these symptoms.

CASE HISTORIES

So that the practical diagnostic significance of these cellular exudate studies may be brought out more clearly, groups of case histories have been selected which will be illustrated with photomicrographic slides of the cellular

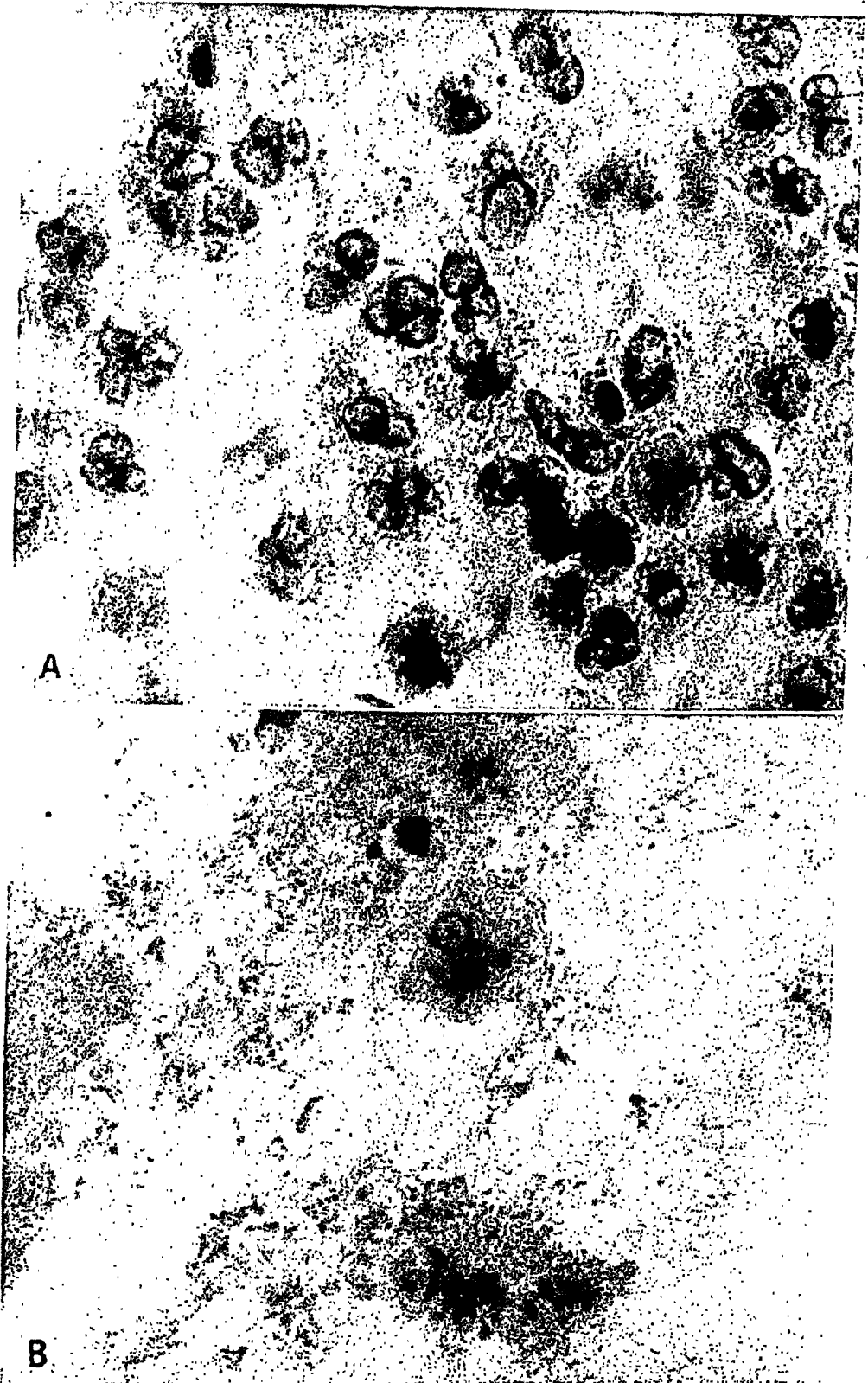


FIG. 3. Exudates of bacillary dysentery compared with amebic dysentery. *A.* Bacillary dysentery (Flexner). Loeffler's methylene blue wet preparation. Note heavy cellular exudate of polymorphonuclear leukocytes and denuded epithelial cells. *B.* Amebic dysentery. Wet fixation in Schaudinn's fluid, Heidenhain's iron-hematoxylin stain. Note trophozoite of *Endameba histolytica* and lack of cellular exudate as compared with *A.* Oil immersion.

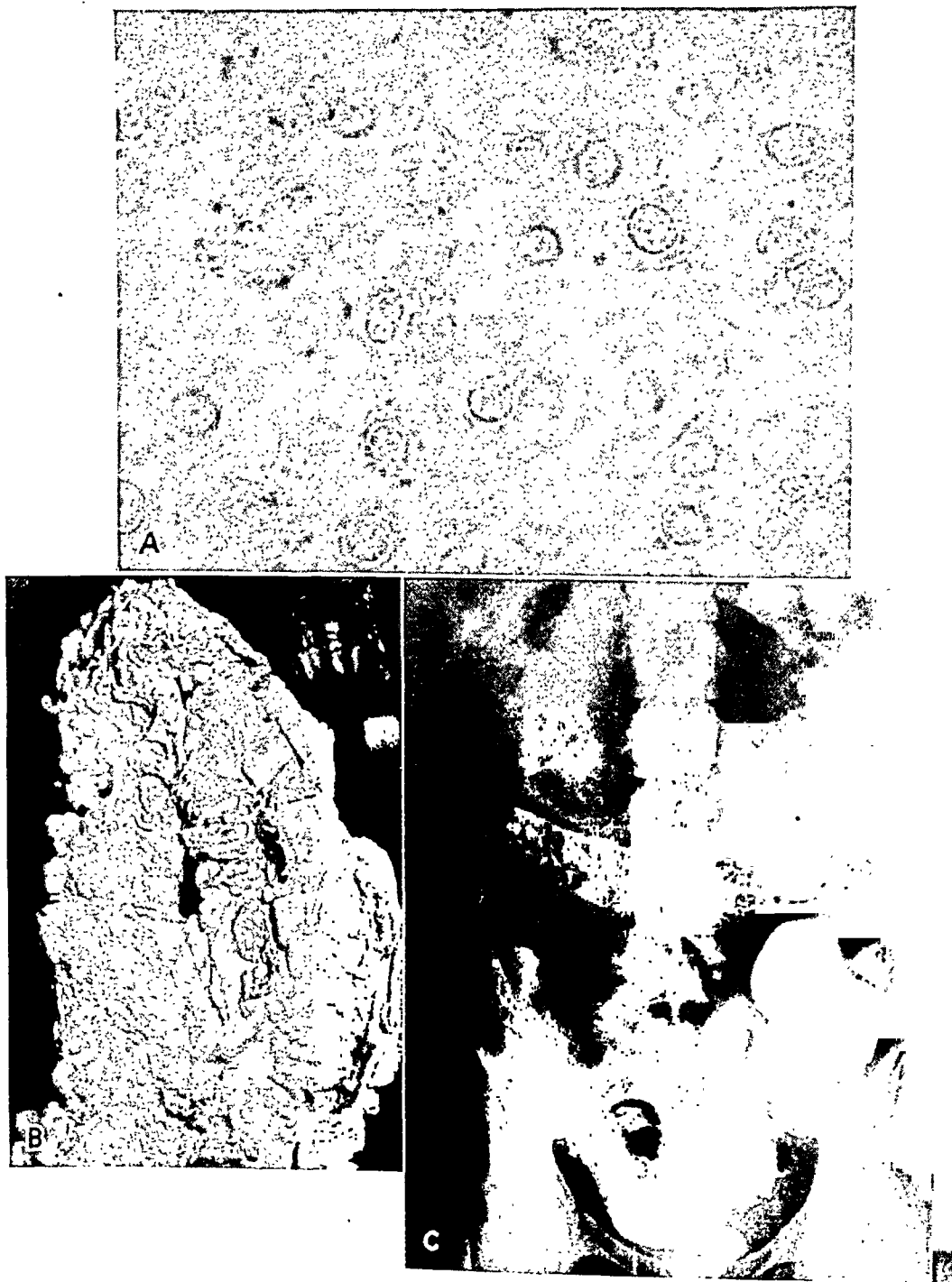


FIG. 4. Chronic ulcerative colitis with hypertrophic polypoid changes. *A.* Cellular exudate in bowel discharge. Loeffler's methylene blue wet preparation. Note irregularly shaped epithelial cells with heavy ringed nuclei. *B.* Autopsy specimen showing polypoid changes in bowel wall. *C.* Barium colon enema roentgenogram.

exudates as they occurred, and in some cases with copies of roentgenograms, photographs of autopsy specimens and surgical specimens. These are all original.

GROUP I

Chronic Ulcerative Colitis with Hypertrophic Polypoid Changes.

Female, aged 22. Four days post-partum, there was sudden onset of diarrhea, 30 to 40 times daily and of hectic fever. Seen for the first time on July 3, 1937, twelve weeks after the onset. There was a heavy cellular exudate of polymorphonuclear leukocytes, and macrophage cells were scattered throughout. The patient continued to have a stormy course, with diarrhea varying from 4 to 5 bowel movements to 15 or 20 in the 24 hours. Four months later, stool examinations still showed a heavy cellular exudate (figure 4) composed chiefly of large irregular-shaped cells with prominent vacuolated nuclei. The clinical condition was essentially the same, except for the fact that the patient's general condition was worse than before. The roentgenologic conclusion, following a barium colon enema on November 16, 1937, was an ileo-colitis with advanced hypertrophic and chronic inflammatory changes as well as probable multiple ulcerations. At autopsy, the colon was found to be markedly hypertrophic with numerous polypi and ulcerations.

This case is typical of the results of cellular exudate studies in cases of chronic ulcerative colitis with hypertrophic changes in the mucosa. In two of the cases, autopsy specimens confirmed the diagnosis made before death.

GROUP II

Patients with Diarrhea and Negative Cellular Exudates.

Female, aged 42, complaining of diarrhea. This patient is the unhappy wife of a man who makes frequent trips to Europe without her. The symptom of diarrhea begins when her husband sails. She is actively interested in a large number of civic and welfare organizations. She noted that her menstrual periods were irregular and that she had frequent hot flashes. Five watery specimens of bowel discharge, following a dose of epsom salts, were negative for cells when examined. Sigmoidoscopy showed that the mucosa of the rectum was atrophic, but further up in the sigmoid, the atrophy was much less pronounced. Fluid aspirated through the sigmoidoscope with the sigmoid cannula was also negative for cellular exudates.

In this type of case, the patients complain of diarrhea of varying degrees of severity, but careful study has failed to reveal the presence of cellular exudates. In each instance, definite elements of stress and strain enter into the picture which in themselves are sufficient to be definitely related as a causal factor to the diarrhea. The administration of sedatives has been followed by prompt relief from the symptoms in each of these patients. It was possible to inform them that they had no ulceration of the bowel, and that the diarrhea was of a type related to nervous stress and strain and was not of the type found in ulcerative colitis. The lack of cells in the diarrheal discharges eliminates the possibility of cancer, and this is of importance to the physician because many patients form an idea that they may have cancer.

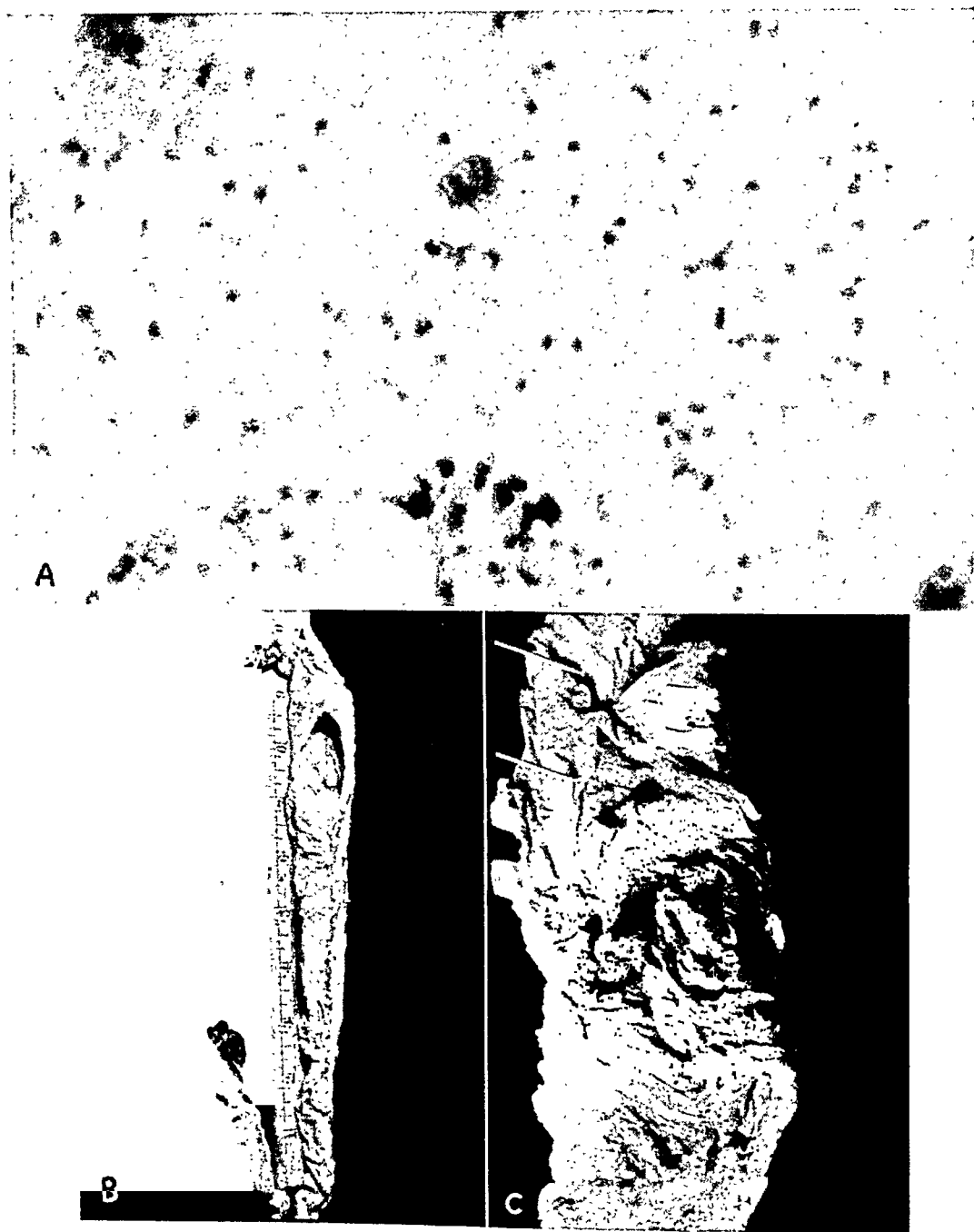


FIG. 5. Acute amebiasis complicated by perforation. A. Bowel discharge showing moderately heavy cellular exudate with *Endameba histolytica*. Wet fixation in Schaudinn's fluid iron hematoxylin stain; high dry. B. Cast of bowel passed by patient three days after admission to hospital. C. Autopsy specimen of portion of colon showing two perforations.

With the knowledge that there is no pathological change when there are no cells in the bowel discharges, he is in a position to reassure his patients and to restore their confidence. The lessening of fear and of nervous tension will often help to reduce the amount of diarrhea.

GROUP III

Patients with Acute Amebic Dysentery.

Female, aged 62, stated that about 10 days prior to her examination she had developed some looseness of the bowel for about 5 days and had passed about a teaspoonful of mucus. Her symptoms were quite insignificant, but because she and her husband had lived in Mexico for many years and because her husband had been found to be infected with *Endameba histolytica*, she was given a saline laxative and her stools were examined. All specimens were negative for cells, but motile forms of *Endameba histolytica* were found. (Figure 3B.)

The typical picture of acute amebic dysentery infestation with no cellular exudate was seen in this patient, and it could be stated with confidence that the only involvement of the bowel was that which was related to the presence of *Endameba histolytica*.

GROUP IV

Acute Amebiasis Complicated by Perforation.

Male, aged 35, chronic alcoholic who complained of diarrhea of six weeks' duration. Blood and mucus were passed with the diarrheal discharges. When first seen the patient was in extremis. The abdomen was distended, tympanic, fever was up to 105°, and there were 31,000 leukocytes. Examination of the stool revealed a moderately heavy cellular exudate, scattered among which were numerous *Endameba histolytica* (figure 5A). The day following the first examination, the patient passed a cast of the bowel (figure 5B) and died 48 hours later. At autopsy, the findings were confluent ulcerations of the entire large intestine and rectum with perforation and generalized fibrinous peritonitis (figure 5C, autopsy specimen).

This case represents that group of amebic dysentery in which complications have arisen through damage to the bowel wall other than that which is caused by the invasion of *Endameba histolytica*. The bowel wall may be damaged by various bacteria, such as the bacillary dysentery group of organisms, by toxic agents, etc. In this patient, stool examination showed not only the presence of *Endameba histolytica* but also evidence of complications in the heavy cellular exudate, which does not ordinarily appear in cases of amebiasis.

GROUP V

Bacillary Dysentery.

Male, aged 14, had a history of sudden onset of diarrhea in the middle of the night with marked tenesmus and passages from the bowel every few minutes. Examination of freshly passed specimens of the bowel discharges were negative for

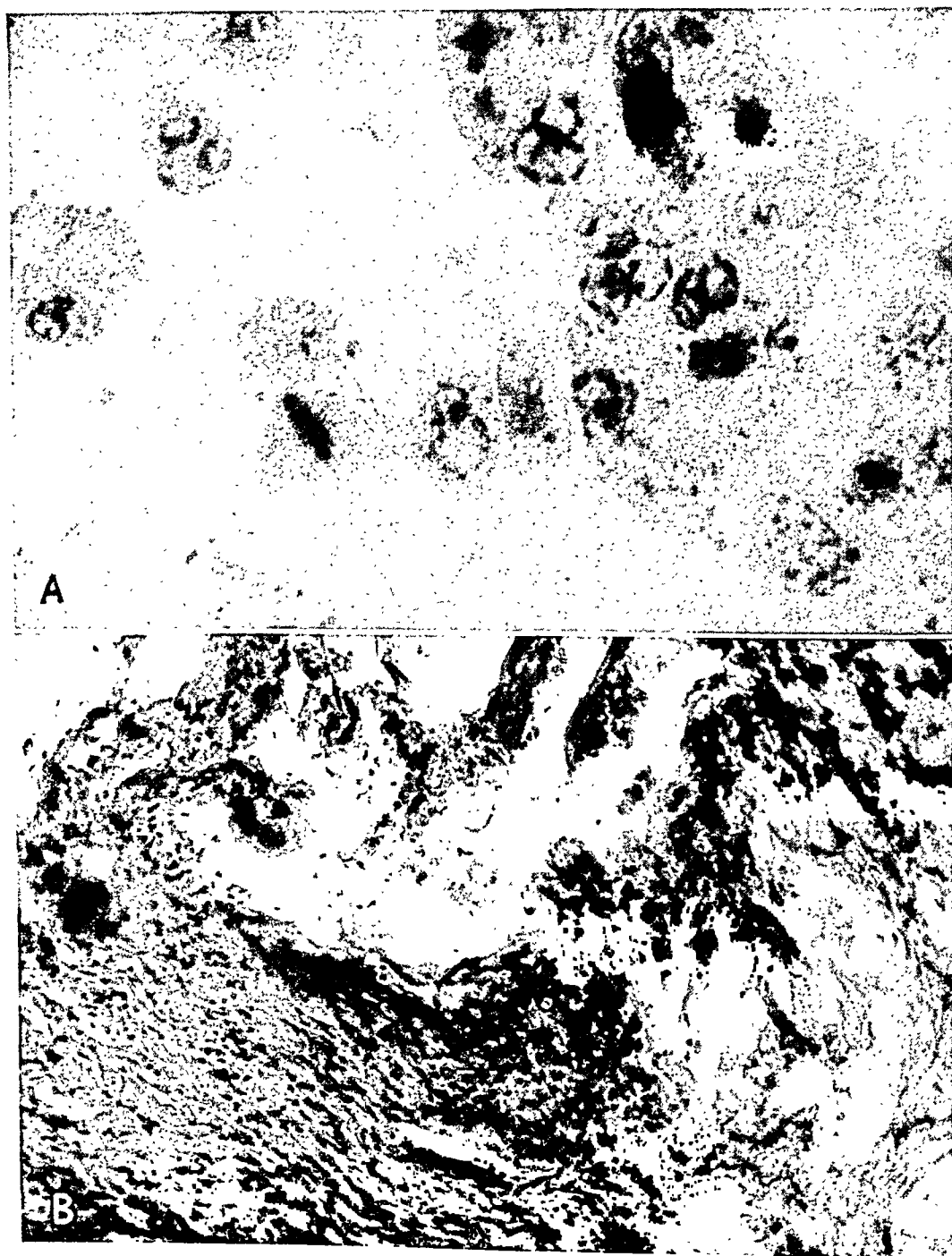


FIG. 6. Carcinoma of the sigmoid colon. *A*. Degenerate epithelial cells in bowel discharges. Loeffler's methylene blue wet preparation; oil immersion. *B*. Section through carcinoma removed at operation.

Endameba histolytica, but showed a heavy cellular exudate typical of bacillary dysentery (figures 2 and 3A). Sigmoidoscopy showed that the bowel mucosa had the usual acute bacillary dysentery appearance. Cultures of the bowel discharges were positive for the Flexner group of organisms. In this case it was possible to culture the bacillary organisms owing to the fact that the onset of the condition was only about 48 hours prior to the time of culture. If the patient has been ill for many days or for weeks, it is not always possible to secure a positive culture.

In these cases the microscopic examination of the stools was important as it gave an indication of the type of pathological condition to be looked for when sigmoidoscopy was performed. The microscopic examination of the stools also gave definite indication of the lines of therapy to be followed.

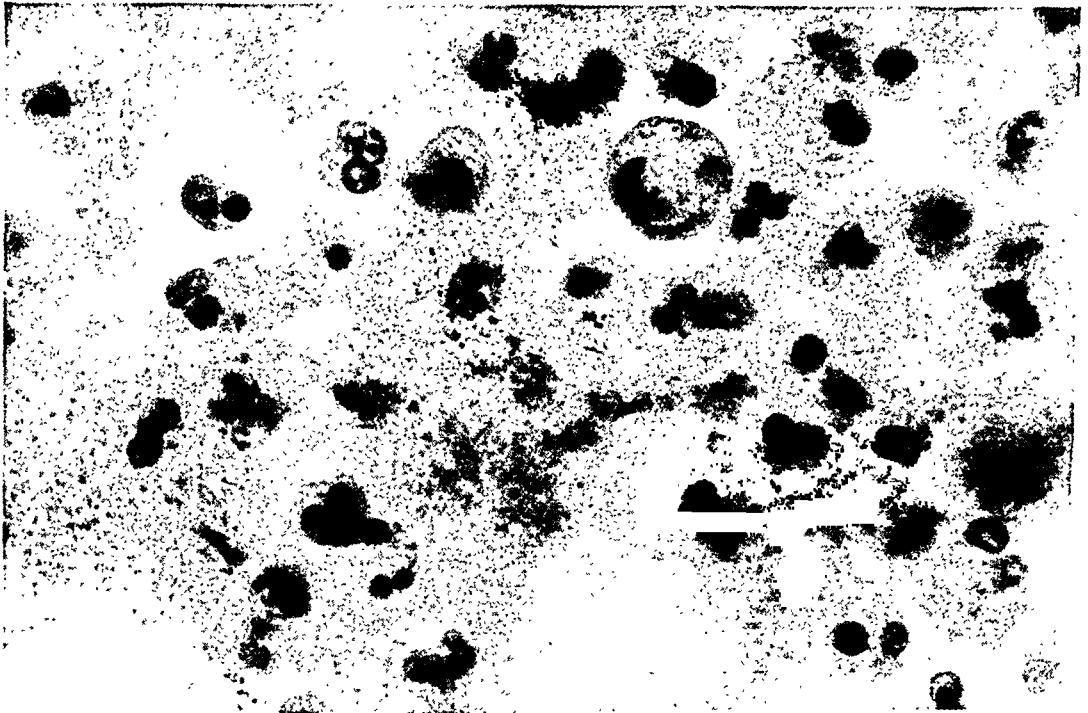


FIG. 7. Cellular exudate from patient with lymphogranuloma venereum of the rectum. Wet fixation in Schaudinn's fluid, Heidenhain's iron hematoxylin counter-stained with eosin; oil immersion.

GROUP VI

Carcinoma of the Sigmoid.

Male, aged 48, referred from Haiti because of diarrhea which had been present for seven months. He passed only four to five stools in the 24 hours, and stated that now there was no blood or mucus present. He had seen blood previously, but his physician had treated him as a case of amebic dysentery owing to the prevalence of that condition in the locality in which he lived. The patient had lost about 23 lbs. in the seven months. He noticed that he did not have good control of his bowel movements. When his symptoms did not respond to antiamebic therapy, he was regarded as a case of "nervous diarrhea," of "sprue," or as a possible infectious type of

colitis which required "disinfection of the intestine." Examination of the bowel discharges was negative for amebae, but showed a heavy cellular exudate of degenerate epithelial cells (figure 6). Sigmoidoscopy showed a carcinoma of the sigmoid (figure 6) which was removed by Dr. R. Franklin Carter.

In this patient, the examination of stools showed the presence of heavy cellular exudates. These findings led to the sigmoidoscopic examinations which revealed the true nature of the pathological conditions from which the patient was suffering. The seriousness of the pathological conditions found in this case indicates the importance of making an immediate examination of the bowel discharge for every patient who complains of diarrhea. If blood and mucus are present, and a preliminary examination of the stools does not reveal the presence of cells, the patient should be given three enemas, following each other without delay, or a colonic irrigation, and the mucus evacuated at the conclusion of this treatment should be collected for examination. If a pathological condition is present, the cells should then be manifest. When cells of any type are found in any of these specimens of bowel discharge, the physician must exhaust every means within his power to discover the true nature of the pathological condition present. There is no other way of relieving suffering and prolonging life.

GROUP VII

Lymphogranuloma Venereum.

Female, aged 42, referred for diagnosis because of complaint of alternating constipation and diarrhea for about four months, with severe pain in the rectum. This patient was given instillations of warm oil in order to relieve the pain. When she was not constipated she had a definite diarrhea with tenesmus and this was accompanied with the almost constant passage of creamy mucus from the rectum. Examination of the bowel discharges revealed the presence of a heavy cellular exudate (figure 7). At sigmoidoscopy, the mucosa was found to be soft velvety and pale pink for about 3 cm. From that point onward numerous small red masses were found, each one of which was perfectly round. These masses were separated from each other, and in the intervening spaces the bowel mucosa presented a normal appearance. The masses were hard and red, and measured about 3 to 4 mm. in diameter. They did not bleed and did not have ulcerated surfaces. They appeared to line the entire rectum, and became more numerous higher up until at 7 cm. from the anus, the bowel became so narrow that it was impossible to pass the sigmoidoscope further. The Frei test was strongly positive. Since beginning the treatment of the patient with the Frei antigen, the symptoms have begun to recede.

In this case, the heavy cellular exudate which was found to be present gave an indication that pathological changes were taking place. Further investigations helped in the determination of the diagnosis.

GROUP VIII

Carcinoma of the Splenic Flexure of the Colon.

Female, aged 62, complained of pain in the abdomen and of blood in the bowel discharges. Her symptoms had been present for two months. The abdomen was

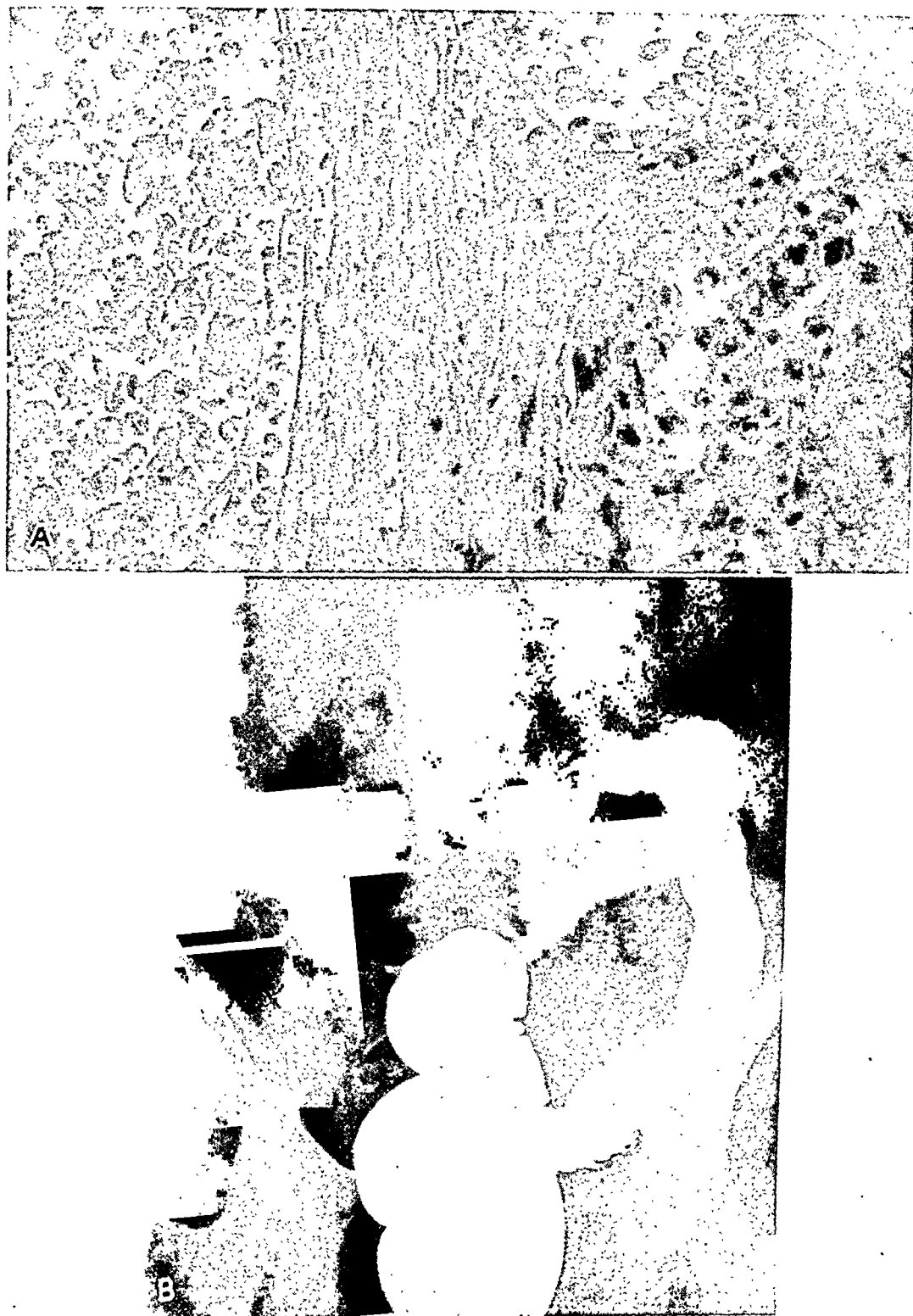


FIG. 8. Carcinoma of the splenic flexure of the colon. *A*. Section through tumor removed at operation. The cells of the bowel discharge were so degenerate that photography was impossible but they appeared similar to those seen in this section. *B*. Barium colon enema roentgenogram.

sore to the touch. She stated that six years previously she had suffered an attack of diarrhea in the course of which she passed as many as 20 bowel movements in the 24 hours. At that time she was told that she was not digesting starches and sugars properly. She also stated that she was now constipated, but that she finally had about three bowel movements daily, through the use of enemas. Without the enemas, she had no bowel movement at all. As a rule there was no result from the first enema, but she developed a sense of pressure in the abdomen and after the second enema the bowels moved. Blood has been present in the bowel movements for about two months. This symptom was coincident with the onset of the abdominal pain for which she was referred. Sigmoidoscopy showed that the bowel mucosa was soft velvety and pale pink, but examination of the mucus aspirated through the sigmoidoscope revealed the presence of a heavy cellular exudate. Roentgen-ray examination with the barium colon enema showed retardation of the barium at the splenic flexure. Laparotomy by Dr. William F. MacFee revealed a large tumor of the splenic flexure of the colon, and the pathological diagnosis was adenocarcinoma of the splenic flexure (figure 8).

GROUP IX

Pathological Changes of the Terminal Ileum.

Male, aged 54, referred because of the complaint of diarrhea for one year, with an average of five to eight bowel movements every 24 hours. Loss of weight amounted to 45 lbs. in the past six months. The patient stated that there was not at any time any blood present in the diarrhea. Examinations of the freshly passed warm specimens of stools were negative for amebae and also for cellular exudates. The patient was prepared for sigmoidoscopy with tepid normal saline enemas. The examination showed that the mucosa was generally edematous, only moderately inflamed and slightly atrophic. A few submucous hemorrhagic areas were present. Mucus aspirated through the sigmoidoscope showed a heavy cellular exudate, and the conclusion from roentgenological studies was "diffuse inflammatory process involving the coils of the terminal ileum associated with polypoid changes."

SUMMARY AND CONCLUSIONS

These case histories, which have been summarized briefly, fall into nine typical groups. In all instances, the patients complained of diarrhea. Cellular exudate studies were made in all cases. With the information obtained from these studies, it was possible to determine whether or not the patients had pathological conditions of the bowel mucosa. In view of the extensive investigations into the validity of these cellular exudate studies, a brief description as well as the findings of which have been given, it is demonstrably safe for the physician to act on the principle that when cells are not found in the bowel discharge after exhaustive and painstaking search, there is no pathological change present; but whenever cells are found, their presence indicates that pathological changes are taking place in the bowel mucosa. Further investigation, with the sigmoidoscope and roentgen-ray, if necessary, must be undertaken immediately in order to locate and identify the pathological condition which the presence of cellular exudate in the bowel discharges shows to exist.

The microscopic examination of the bowel discharge for the presence or absence of cellular exudate is therefore the first step to take for diagnosis and for the subsequent treatment of every patient who is suffering from any of the symptoms associated with bowel complaint.

BIBLIOGRAPHY

1. BERCOVITZ, Z.: The new sigmoid cannula, *Am. Jr. Digest. Dis. and Nutr.*, 1936, iii, 499-500.
2. BERCOVITZ, Z.: Studies in cellular exudates of bowel discharges. I. Control observations in 1123 patients, 7 autopsies and 3 dog specimens, *Jr. Lab. and Clin. Med.*, 1940, xxv, 788-795.
3. BERCOVITZ, Z., and FULLER, C. C., to be published.

THE RÔLE OF CORONARY ARTERY DISEASE IN THE ETIOLOGY OF AURICULAR FIBRILLATION *

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THE prevailing views concerning the rôle of coronary artery disease in the etiology of auricular fibrillation appear contradictory. Although its ultimate cause remains obscure, this arrhythmia is known to be associated with certain clinico-pathological states to which a greater or lesser degree of etiological significance is generally ascribed and among which coronary artery disease is frequently included.^{1, 2} On the other hand, it is well known that auricular fibrillation and angina pectoris of coronary origin occur together but rarely, and it has been suggested that these two conditions are more or less incompatible.^{1, 2, 3} Furthermore, although transient auricular fibrillation develops quite commonly during the early course of acute coronary occlusion, the rarity with which acute coronary thrombosis occurs in cases of established auricular fibrillation has been noted by many observers.^{3, 4} It thus appears that with respect to auricular fibrillation, coronary artery disease is regarded at the same time as of both causative and preventive significance. For the purpose of shedding some light upon this apparent paradox the following investigation was carried out.

(A) The records of 100 consecutive cases which came to autopsy with a clinical diagnosis of auricular fibrillation were analyzed to determine (1) the underlying pathological lesions, (2) the average age at death, (3) the degree of cardiac decompensation, and (4) the degree of coronary atherosclerosis. The degrees of decompensation and of coronary sclerosis were for convenience graded as 1, 2, 3, and 4, signifying respectively, moderate, moderately severe, severe, and extreme. The results of this analysis which are recorded in table 1 may be summarized as follows:

TABLE I
100 Cases of Auricular Fibrillation

Underlying Pathological Lesion	No. of Cases	Age	Cardiac De-compensation*	Coronary Sclerosis*	Blood Pressure	Heart Weight
Acute coronary occlusion	9	71.5	3.5	3.75	167/101	466
Toxic thyroid	6	66.1	3.25	1.0	156/85	400
Rheumatic endocarditis	23	48.5	3.43	1.05	143/88	600
Luetic aortitis	1	38.0	4.0	—	130/?	700
Others	61	68.7	3.40	2.29	166/104	600
Total or Average	100	63.8	3.42	2.06	161/100	576

* On a scale of 0 to 4.

* Received for publication July 10, 1939.

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The average age was 63.8 years, the average degree of decompensation was 3.40 or a grade between severe and extreme, and the degree of coronary atherosclerosis was on the average 2.06 or only moderately severe. The only instances of severe to extreme grade of coronary atherosclerosis (3.22) were noted in the group of nine cases of acute coronary thrombosis in which it seemed probable that the arrhythmia appeared for the first time after the acute occlusion.

An examination of the underlying pathological lesions revealed that in 38 of the cases the auricular fibrillation was associated with those clinico-pathological states which are known to have some influence upon the development of this arrhythmia. However, in 61 of the cases the only disturbances found were (1) clinically, a high degree of congestive failure (3.42) with a significantly elevated blood pressure, and (2) pathologically, varying degrees of cardiac enlargement (average weight 576 gm.) with a moderately severe grade of coronary sclerosis (2.29). In addition there was one case of luetic aortitis in which auricular fibrillation developed in association with an extreme degree (grade 4) of cardiac decompensation although the coronary arteries (including their orifices) were entirely free from disease.

(B) For comparison, in order to determine whether this moderately severe grade of coronary sclerosis may be viewed as of etiological importance in the genesis of the associated auricular fibrillation, an analysis was made of the records of a second series (table 2) of 100 consecutive cases which came to autopsy with a clinical diagnosis in which the rhythm was stated to be "regular" or "sinus," and in which the average age at death (69.7) approximated that of the 61 cases referred to above (68.7).

TABLE II
100 Cases with Sinus Rhythm

No. of Cases	Average Age	Cardiac Decompensation*	Coronary Sclerosis*	Blood Pressure	Heart Weight
100	69.7	1.13	2.01	146/85	394

* On a scale of 0 to 4.

An examination of the data so obtained and recorded in table 2 shows that the average grade of coronary sclerosis present in the 100 cases with regular or sinus rhythm was 2.01 or but slightly lower than that found in the 61 cases with auricular fibrillation recorded in table 1. On the other hand the grade of congestive failure in the non-fibrillating cases of Series II was only 1.13 or much less than the high degree (3.40) of failure present in the 61 cases with auricular fibrillation of Series I.

Further comparison of the two tables discloses two other important differences. The blood pressure values and heart weights which were within normal limits in non-fibrillating cases (Series II) were found significantly

increased in those with the abnormal rhythm (Series I). The thought, therefore, suggests itself that hypertension, congestive failure and cardiac enlargement rather than coronary sclerosis might be the important factors in the genesis of auricular fibrillation.

(C) The records of a third group of 100 consecutive cases were chosen for analysis within the same age group (table 3). In the selection of this

TABLE III
100 Cases Selected to Indicate Relation of
Age to Incidence of Coronary Sclerosis

No. of Cases	Average Age	Coronary Sclerosis*
100	67.9	2.46

* On a scale of 0 to 4.

series no attention was paid to the diagnosis or the character of the cardiac rhythm. The information desired in connection with the examination of this third series of records was the influence of "age" upon the incidence of coronary sclerosis independent of the presence or absence of auricular fibrillation. It will be seen from an examination of table 3 that the average grade of coronary sclerosis for this group (average age 67.9) was 2.46 or even slightly higher than that found in the 61 cases with auricular fibrillation belonging to Series I. This observation suggests the thought that the coronary sclerosis noted in the 61 cases of Series I was related to the advanced age rather than to the auricular fibrillation.

(D) A fourth series of records of 100 autopsied cases (table 4) was selected for study from approximately the same age group (average age

TABLE IV
100 Cases, Some with Sinus Rhythm and Some with Auricular Fibrillation

Rhythm	No. of Cases	Average Age	Cardiac Decompensation*	Coronary Sclerosis*
Auricular fibrillation	19	71.2	3.16	2.00
Regular	81	70.4	1.09	2.148
Total or Average	100	70.5	1.47	2.122

* On a scale of 0 to 4.

70.5 years). This series of 100 consecutive cases chosen on the basis of age was analyzed with respect to (1) the character of the cardiac rhythm, (2) the degree of coronary sclerosis and (3) the degree of congestive heart failure. In 19 cases auricular fibrillation was noted and in 81 cases the rhythm was reported as having been regular or sinus. As will be seen from an examination of table 4 the degree of coronary sclerosis for the 19 cases with auricular fibrillation was no greater or even a little lower (2.00) than

that recorded for the 81 cases with regular or sinus rhythm (2.148). On the other hand the grade of congestive failure noted in the 19 cases with auricular fibrillation was much higher (3.16) than that observed in the 81 cases with regular or sinus rhythm (1.09).

(E) Finally, a fifth series of records was examined for the purpose of confirming the fact now generally recognized that auricular fibrillation occurs but rarely in cases of angina pectoris. This group consists of the records of patients under active treatment for whom there was made a diagnosis of angina pectoris on the basis of coronary artery disease. As will be seen from an examination of table 5, auricular fibrillation was noted in only five cases in all of which a high grade of congestive failure was present. The degree of decompensation noted in the five fibrillating cases was 3.4 compared to a grade 1.3 for the non-fibrillating cases.

TABLE V
100 Cases of Angina Pectoris of Coronary Origin

Rhythm	No. of Cases	Average Age	Cardiac Decompensation*	Blood Pressure
Auricular fibrillation	5	69.0	3.4	135/89
Regular	95	61.0	1.30	158/91
Total or Average	100	61.4	1.41	157/91

* On a scale of 0 to 4.

COMMENT

The results of the foregoing analyses would seem to indicate that coronary sclerosis bears no direct relationship to the development of auricular fibrillation. The degree of sclerosis noted in cases with auricular fibrillation was no greater than that observed in persons of a similar age group in whom the rhythm was "regular" or "sinus." On the other hand a definite relationship was observed between this arrhythmia and congestive failure; the degree of the latter was invariably significantly higher in the cases with auricular fibrillation than in those with regular or sinus rhythm. In this connection it was obviously desirable to determine whether symptoms of decompensation preceded the onset of auricular fibrillation. Unfortunately, such determination was not often possible. However, in the few instances (13 cases) in which information bearing on this point was available, the evidence suggested that symptoms of congestive failure (edema or dyspnea) preceded those of auricular fibrillation (palpitation). In four instances the records clearly indicated that on admission there were signs of congestive failure and regular rhythm with the subsequent development of auricular fibrillation.

The evidence herein presented, therefore, appears to suggest that a probable relationship exists between congestive failure and auricular fibrilla-

tion, but that coronary sclerosis, except insofar as it may be concerned in the production of congestive failure, cannot be regarded as an etiological factor in the genesis of auricular fibrillation. The frequent appearance of transient auricular fibrillation following an attack of acute coronary occlusion may be explained on the basis of an associated congestive failure which, though often in but slight degree, so frequently develops after such an accident. Master, Dack and Jaffe⁵ in a study of 300 cases of coronary artery thrombosis noted that the incidence of increased arterial tension, enlarged heart and congestive heart failure was definitely greater among these cases which developed auricular fibrillation than in the control group. It is also noteworthy that in experimental ligation of the coronary arteries in animals, which operation frequently results in various types of cardiac arrhythmias, auricular fibrillation and flutter are rarely encountered.^{5, 6}

Although in the various series of cases described above there was not observed a single instance in which auricular fibrillation was noted in the absence of congestive failure, it is, of course, well known that such cases do occur, especially in the presence of mitral stenosis, thyrotoxicosis, or hypertension. The exact mechanism involved in the production of the arrhythmia under such circumstances is not known. However, it is probable, at least in the cases with mitral stenosis, that the stretching of the left auricle is a major factor. This possibility is also applicable to the cases of hypertension where distention of the left auricle due to increased intra-auricular pressure may result in auricular fibrillation even before there is gross evidence of failure of the left ventricle.

If the concept that distention of the left auricle is an important factor in the initiation of auricular fibrillation proves valid it will afford an explanation for the interesting clinical observation that auricular fibrillation is so rare in isolated failure of the right side of the heart arising from pulmonary heart disease^{7, 8, 9}; for in this type of congestive heart failure, though the right auricle is often markedly dilated and hypertrophied the left auricle remains normal or even smaller than normal.

The above observations concerning the rôle of coronary artery disease in the etiology of auricular fibrillation are not altogether original. Essentially similar investigations with like results were reported by Cookson¹⁰ in 1930 and Brown¹¹ in 1935. However, the present effort appears justified by the frequent inclusion of coronary sclerosis among the etiological factors of auricular fibrillation noted in the current literature and in recent textbooks.

The question involved is not solely of academic interest; its practical implications concern both diagnosis and prognosis as illustrated in the following observation.

A woman, 42 years of age, without any signs of antecedent congestive failure, suddenly developed persistent auricular fibrillation. After a period of two months without adequate treatment, severe congestive failure supervened. The electrocardiogram confirmed the presence of auricular fibrillation, but indicated otherwise normal

ventricular complexes. Because of the high degree of congestive failure, and since a careful investigation excluded hyperthyroidism and rheumatic or hypertensive heart disease, a diagnosis of coronary artery disease as the underlying etiological factor received serious consideration and an unfavorable prognosis was implied. However, under proper management including adequate digitalization the signs of congestive failure rapidly disappeared, and normal rhythm was readily restored by means of quinidine. Rapid and complete recovery ensued with resumption of normal activity without further treatment. Three years later the patient continues to enjoy perfect health.

In the light of the observations recorded in this communication coronary artery disease might well have been excluded from consideration in the above-described case in favor of a diagnosis of "functional auricular fibrillation" with a favorable prognosis now fully justified by subsequent developments.

SUMMARY AND CONCLUSIONS

A. Data obtained from an examination of the records of 400 autopsied cases tend to suggest that:

1. In the absence of congestive heart failure or acute coronary occlusion, coronary artery disease is not a cause of auricular fibrillation.

2. Congestive heart failure involving the left side of the heart, regardless of the underlying pathological lesion, tends to favor the development of auricular fibrillation. It is suggested that stretching of the left auricle might be an important factor in this process.*

3. Coronary artery disease, although not a direct cause of auricular fibrillation, nevertheless may be concerned indirectly in the genesis of the arrhythmia by first inducing congestive failure. This mechanism is offered as a probable explanation for the frequent appearance of transient auricular fibrillation following an attack of acute coronary thrombosis, although this arrhythmia occurs very rarely in angina pectoris of coronary origin prior to the onset of congestive failure.

4. In a case already in congestive failure, the subsequent appearance of auricular fibrillation affords no additional information which might serve as an aid in determining the presence or the absence of coronary artery disease.

B. An analysis of the records of 100 cases of angina pectoris under active treatment confirms the observation already noted by many authors that auricular fibrillation is rare in angina pectoris of coronary origin, except in the presence of congestive failure.

* The effect of failure of the left ventricle upon the left auricle is often indicated by changes in the electrocardiogram relating to auricular activity, which are strikingly similar to those occurring in mitral stenosis. These changes which are believed to be due to hypertrophy and dilatation of the left auricle consist of a widened P-wave of low voltage, usually bifid or flat-topped. They have been recently described by Wood and Selzer¹² as a new and early sign of left ventricular failure.

REFERENCES

1. LEVINE, S. A.: Clinical heart disease, 1936, W. B. Saunders Company, Philadelphia and London, pp. 212 and 114.
2. LEWIS, THOMAS: Diseases of the heart, 1937, The Macmillan Company, New York, pp. 81 and 50.
3. LEVINE, S. A.: Coronary thrombosis: its various clinical features, *Medicine*, 1929, viii, 278-279.
4. BEAN, W. B.: Infarction of the heart. II. Symptomatology of acute attack, *ANN. INT. MED.*, 1938, xi, 2090.
5. MASTER, A. M., DACK, SIMON, and JAFFE, H. L.: Disturbances of rate and rhythm in acute coronary artery thrombosis, *ANN. INT. MED.*, 1937, xi, 735.
6. OTTO, H. L.: The extracardiac nerves. IV. An experimental study of coronary obstruction, *Am. Heart Jr.*, 1928, iv, 64.
7. ROSENBLATT, M. B.: Paroxysmal auricular fibrillation in the course of right heart failure due to chronic pulmonary tuberculosis, *Am. Heart Jr.*, 1938, xv, 114.
8. WHITE, PAUL: Heart disease, ed. 2, 1937, The Macmillan Company, New York, p. 339.
9. SMITH, K. S.: The heart in pulmonary disease, *Post-Grad. Med. Jr.*, 1930, vi, 43.
10. COOKSON, H.: The etiology and prognosis of auricular fibrillation, *Quart. Jr. Med.*, 1930, xxiii, 309.
11. BROWN, M. G.: The relationship of coronary arteriosclerosis to auricular fibrillation with special reference to the term "arteriosclerotic heart disease," *New England Jr. Med.*, 1935, ccxii, 963.
12. WOOD, PAUL, and SELZER, A.: A new sign of left ventricular failure, *Brit. Heart Jr.*, 1939, i, 81.

THE BALANCE BETWEEN CAPSULAR POLYSACCHARIDE AND ANTIBODY IN RELATION TO THE PROGNOSIS AND THERAPY OF PNEUMOCOCCAL PNEUMONIA *

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INTRODUCTION

THE antigen-antibody balance in pneumococcal pneumonia was first reported by Blake,¹ who employed the methods of detection described by Dochez and Avery.^{2, 3} Blake¹ studied 19 cases and demonstrated capsular polysaccharide in the blood of 11, 10 of whom died. Circulating antibody was not detected in these patients, nor in those who excreted large amounts of capsular polysaccharide in the urine. It has since been shown experimentally that capsular polysaccharide may interfere with defenses against the pneumococcus by enhancing the invasive power of pneumococci (Felton and Bailey⁴; A. W. Downie⁵), or by blocking the reaction between pneumococcal antigen and homologous antibody (Felton and Bailey,⁴ Sickles⁶).

Although the therapeutic value of specific serum in pneumococcal pneumonia has been well established,^{7, 8, 9, 10, 11, 12} its effectiveness in the presence of capsular polysaccharide has not been investigated. The introduction of sulfapyridine provided an additional impulse to make further correlations between the immunological responses in pneumonia and recovery. Our particular interest was directed towards noting the comparative influence of sulfapyridine, specific serum, or the combination, on the antigen-antibody balance, and its relation to the outcome of therapy. In a previous communication¹³ we briefly summarized the results of our studies of 25 cases, describing two cases, and recording observations suggesting that sulfapyridine alone may be ineffective in the presence of free circulating capsular polysaccharide. It is the purpose of this report to analyze the 25 cases, to add our later observations on one (W. L.), and on a twenty-sixth case observed during the course of the analysis.†

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† During the course of analysis of this series, an additional case of pneumococcus type III pneumonia, bacteremic, in whose blood capsular polysaccharide was detected, came under observation. This patient, treated with sulfapyridine alone, recovered after a stormy course, capsular polysaccharide continuing to be detectable in the blood for a period of 10 weeks, throughout which time the urine repeatedly contained capsular polysaccharide. During the greater part of her hospital stay, there was roentgenological evidence of a collection of air and fluid in the pleural space of the affected side. This effusion subsided spontaneously, the

METHODS

Since January, 1939, the treatment of pneumonia patients at Harlem Hospital (Pneumonia Service), has been rotated, according to type, to provide the following three series: (1) antipneumococcal serum alone, (2) sulfapyridine alone, (3) antipneumococcal serum and sulfapyridine. On admission, sputum was obtained for immediate typing and a blood culture was taken. As soon as the type was available, the patient was treated according to the group into which he fell. For each antigen-antibody determination, the serum obtained from 15 c.c. of clotted blood was subjected to study within a week of removal. Sera were always refrigerated, without preservative, in corked tubes, until used. Blood cultures were repeated frequently.

(a) *Antigen (capsular polysaccharide) detection*:* Half c.c. quantities of serial dilutions of patient's serum (employing 0.85 per cent saline as diluent) were mixed with 0.5 c.c. of a water-clear $\frac{1}{10}$ dilution of homologous rabbit antipneumococcal serum, having an original antibody titer of 5,000 to 10,000 units per c.c. Final dilutions of patient's serum obtained were 1 to 2; 1 to 4; 1 to 8; and 1 to 16. (b) *Precipitin detection*: Half c.c. of the "optimal" saline dilution (previously determined for each type) of capsular polysaccharide, prepared from stock saline solutions of 1-1,000 or 1-5,000 concentration, were mixed with 0.5 c.c. of serially diluted patient's serum. Final dilutions of patient's serum were also 1 to 2; 1 to 4; 1 to 8; and 1 to 16. (c) *Agglutinin detection*: Half c.c. of saline suspensions of the sediment from 18 hour broth cultures, giving an evident specific Neufeld reaction, were mixed with 0.5 c.c. serial dilutions of patient's serum; dilutions were carried to 1 to 64. (d) *Controls*: These consisted of half c.c. of patient's serum with (1) 0.5 c.c. of heterologous antipneumococcal rabbit serum and (2) 0.5 c.c. of heterologous polysaccharide (in appropriate dilution), (3) half c.c. of homologous antipneumococcal rabbit serum plus half c.c. of homologous polysaccharide; (4) half c.c. of homologous antipneumococcal rabbit serum plus half c.c. of heterologous polysaccharide; (5) 0.5 c.c. of suspension of organisms plus 0.5 c.c. of saline; (6) 0.5 c.c. of homologous antipneumococcal rabbit serum plus 0.5 c.c. of saline; (7) 0.5 c.c. of homologous capsular polysaccharide plus 0.5 c.c. of saline.

All mixtures were made in 10 by 75 mm. precipitation tubes. The tubes were placed in the water bath at 37° C. for 2 hours, and then refrigerated overnight. Reactions were read after the period of refrigeration.†

Positive precipitative reactions varied from a fine cloud to a granular precipitate. An occasional "button" type of precipitate was observed.¹⁴ Controls, both positive and negative, were always in order.

Sulfapyridine Therapy: The initial dose of sulfapyridine was 5 grams, followed by 1 gram 4-hourly, day and night until the temperature had been normal or below 100° F. for three consecutive days. In some instances treatment was continued for as long as 10 days and occasionally given in several courses. Blood for sulfapyridine concentration was obtained on the morning following commencement of treatment,

patient remaining afebrile during the last several weeks. The patient was discharged from the hospital 10 weeks ago, has been followed at regular intervals and is still clinically well. Her blood and urine have been negative for capsular polysaccharide for at least six weeks. This case will be included in the numerical analysis which follows.

* The methods of detection employed for these 26 cases are those originally used by Dochez and Avery and by Blake. Further observations in our laboratories indicate that the sensitivity of detection of capsular polysaccharide can be increased by mixing equal quantities of undiluted patient's serum with the "optimal" dilution of type-specific antibody solution. These "optimal" dilutions have been determined for the different pneumococcal types studied.

† We have been able to increase the rapidity and sensitivity of all the reactions by employing high-speed centrifugation instead of the usual procedure.^{14, 15}

and at 48-hour intervals thereafter. Sulfapyridine concentrations were determined with an optically balanced two-celled, photoelectric colorimeter.

Serum Therapy: Either horse or rabbit sera or both were employed in therapy, rabbit serum having been used in most cases. The majority of patients received between 100,000 and 300,000 units of serum, administered at 2-hourly intervals, intravenously, the usual precautions in testing for sensitivity having been observed. Where bacteremia was discovered or clinical response to the initial dosage of serum was inadequate, additional serum was usually given, the duration of therapy extending, in these cases, to as long as 52 hours.

Serum and Sulfapyridine: Sulfapyridine and antipneumococcal serum, when combined, were used in the same dose employed for those receiving either alone.

RESULTS

The 26 cases were distributed among the following types: I, 8 cases; II, 1 case; III, 8 cases; IV, 1 case; VII, 8 cases. The type was obtained from the sputum in all cases; in 10 patients bacteremia was present. The sera from 16 patients were studied before and after initiation of therapy, while examination of the sera from the remaining 10 was begun immediately after the commencement of therapy.

One hundred and thirty-five series of determinations were carried out in all. Generally, bloods were obtained at daily intervals, immediately after beginning of therapy, until temperature fell to normal or the patient died. The frequency of subsequent determinations varied with the clinical response of the patient, these being at shorter intervals (1 to 3 days) where the response was poor, and at longer intervals where the control of infection was rapidly effective.

(A) *Treatment with Sulfapyridine Alone:* Table 1 summarizes the results obtained in 12 cases treated with sulfapyridine alone. In three cases capsular polysaccharide was detectable in the blood; all were pneumococcus III bacteremias, one with an empyema on admission. Two of these patients died despite attainment of a 2 to 6 mg. per 100 c.c. concentration of sulfapyridine in the blood. The third, as previously mentioned, is apparently well. Antibodies became detectable in the blood of 9 of these 12 patients; agglutinins in all 9, and agglutinins and precipitins in only three.

Of the three patients who failed to develop demonstrable antibodies, two recovered. One of these patients was a pneumococcus I bacteremia, the other an uncomplicated pneumococcus III without bacteremia. Neither of these patients had capsular polysaccharide in the blood.

The third patient, referred to in an earlier communication,¹¹ was a 69-year old negro male, admitted on the fifth day of disease with a pneumococcus III bacteremia. The serum of this patient gave a positive reaction for capsular polysaccharide and he died on the seventh day of disease, despite a blood sulfapyridine concentration of 5.4 and 4.7 milligrams per cent on the sixth and seventh days. Antibody did not develop and there was no appreciable decrease of circulating polysaccharide, although the number of colonies from the blood culture had progressively decreased.

Of the remaining nine patients in whose blood antibodies became de-

TABLE I
Sulfapyridine

Type	Patient	Age (yrs.)	Treatment		Sulfapyridine Concentration in Blood Milligrams %	Serum Titer †		
			Day of Disease when Started	Quantity Grams		Capsular Polysaccharide	Agglutinins	Precipitins
I	119776	12	6th	57	4.8 4.0 3.6	Negative	1:32	1:16
I*	116356	23	6th	39	5.4 5.3	Negative	Negative	Negative
I	115471	27	6th	48	5.1 5.0 5.0 4.3	Negative	1:8	Negative
III	115516	28	9th	26	5.4 6.0	Negative	1:4	Negative
III	116114	39	4th	50	7.4 6.6 5.4 8.6	Negative	1:32	Negative
III	115451	42	3d	34	4.5 3.3 2.6	Negative	Negative	Negative
VII	118813	36	9th	30	4.8 2.4 1.4	Negative	1:64	1:8

* Bacteremia.

† Died.

‡ Highest Titer.

TABLE I—Continued

Type	Patient	Age (yrs.)	Treatment		Sulfapyridine Concentration in Blood Milligrams %	Serum Titer †		
			Day of Disease when Started	Quantity Grams		Capsular Polysaccharide	Agglutinins	Precipitins
VII	116359	55	3d	57	5.4 7.4 6.4 8.0	Negative	1:4	Negative
VII	121215	62	4th	28	5.9 4.8 14.8	Negative	1:16	1:8
III*	122085	45	8th	108	8.0 10.2 4.4 7.6 7.8 9.8 2.6 9.0 12.6	Positive	1:2	Negative
III*	114515†	54	?	16½	4.3 1.8	Positive	1:32	Negative
III*	116164†	69	5th	21	5.4 4.7	Positive	Negative	Negative

tectable, six developed only agglutinins. Five of these patients recovered, one of whom had capsular polysaccharide in the blood, and bacteremia. Two of the recovered patients developed detectable antibodies prior to clinical recovery, while the remaining three patients developed antibodies after clinical recovery. In the urine of three of these patients, all pneumococcus III, capsular polysaccharide had been detectable at the time of febrile elevation. The urine of others was not studied.

The sixth patient in this group died. Capsular polysaccharide was detectable in her blood prior to commencement of therapy. She was a 54-year old female Puerto Rican. Eight weeks before admission to Harlem Hospital, she had been hospitalized elsewhere for a pneumococcal III, right upper lobe pneumonia, non-bacteremic, complicated by diabetes mellitus and moderate ketosis. With neither sulfapyridine nor specific antipneumococcal therapy, she had made an apparent recovery and had been discharged, although there had been evidence of unresolved fluid at the right base at the time. The diabetes had been controlled with some difficulty. For several weeks following discharge, she had been apparently well, but two weeks prior to admission to Harlem Hospital had developed low-grade fever, with chills and generalized aches and pains. On admission she was acutely ill, hyperglycemic, there was a purulent effusion at the right base, and bacteremia, pneumococcus III (45 col. per c.c.). At this time agglutinins were present (1 to 32) and simultaneously capsular polysaccharide. She was promptly given sulfapyridine, but, because of vomiting, received only 16.5 grams in three days. The blood culture became sterile and temperature fell to normal, though the pulse was slightly elevated. At this point sulfapyridine was stopped. Following a thoracotomy which drained poorly, her temperature rose, ketosis progressed, she developed stupor and died on the eighth day of hospitalization, 48 hours after cessation of sulfapyridine.

The last three patients developed detectable precipitins as well as agglutinins; there was no detectable capsular polysaccharide in their blood. All three of these patients recovered. In one of these patients withdrawal of sulfapyridine was followed by temporary elevation of temperature and diminution of precipitin titer. This was followed, in 36 hours, by spontaneous return of normal temperature, increasing antibody titer, and clinical recovery. The observation suggests that some of the febrile reactions which follow withdrawal of sulfonamide compounds represent abortive reinfections due to a short reactivity of residual, unkilld organisms. During this reactivity such organism growth may be productive of enough capsular polysaccharide to neutralize precipitin without itself becoming detectable. In this same patient, pneumococcus VII, X and XVI were found in the sputum. Capsular polysaccharide for type VII alone was detected in his urine. That this was the infecting type was confirmed by the detection, on several occasions, of a type VII precipitin in his blood.

(B) *Treatment with Serum Alone:* Table 2 summarizes the results obtained in eight cases treated with serum alone. In one case capsular polysaccharide was detectable in the blood, a pneumococcus III pneumonia, non-bacteremic. This patient died.

He was a 35-year old negro male admitted on the first day of a single-lobe pneu-

TABLE II
Serum

Type	Patient	Age (yrs.)	Treatment		Serum Titer ‡		
			Day of Disease when Started	Quantity Units	Capsular Polysaccharide	Agglutinins	Precipitins
I*	115803	13	5th	480,000	Negative	1:32	1:16
I	115915	15	7th	160,000	Negative	1:64	1:16
I	116299	37	4th	160,000	Negative	1:64	1:8
II*	117859	60	8th	1,239,000	Negative	1:32	1:16
VII	116181	28	2nd	320,000§	Negative	1:64	1:16
VII*	115698	32	3rd	465,000	Negative	1:32	1:8
IV*	115417†	43	4th	733,000	Negative	Negative	1:16
III	115330†	35	1st	700,000	Positive	1:16	1:4

* Bacteremia. † Died. ‡ Highest Titer. § Horse serum (all others rabbit serum).

monia, pneumococcus III. There was a loud diastolic murmur at the second intercostal space to left of the sternum, and roentgen-ray evidence of marked widening of the ascending aorta, interpreted as syphilitic aortitis with aneurysmal bulge. There was also left ventricular enlargement, and consolidation of the inner portion of the left lung. He was promptly given 700,000 units of type III antipneumococcal rabbit serum. Blood from this patient prior to treatment was negative for both capsular polysaccharide and antibody. On the day following serum therapy, both capsular polysaccharide and agglutinins became detectable and the urine was positive for capsular polysaccharide. On the following day, capsular polysaccharide was no longer detectable, and the antibody titer increased, precipitins appearing as well. Despite the excess of antibody and the disappearance of polysaccharide, he developed a marked tachycardia and persistent fever and died on the fourth day after admission. Postmortem examination by Dr. Solomon Weintraub revealed bilateral lower lobe pneumonia (gray hepatization) with pulmonary edema, syphilitic aortitis and fatty degeneration of the liver. It is difficult to understand why this patient developed detectable polysaccharide only after intravenous serum therapy. The amount detectable in his blood could not have been introduced with the therapeutic serum. It is noteworthy that this patient died despite rapid neutralization of circulating capsular polysaccharide, indication of the severity of infections accompanied by appearance of capsular polysaccharide in the blood stream.

Of the other seven patients, none had capsular polysaccharide detectable in the blood. Six recovered and one patient died. Of the six recovered patients, three were bacteremic. All six had both agglutinins and precipitins in high titer, always detectable in the first blood obtained after injection of the serum. The remaining patient was a pneumococcus IV bacterial endocarditis terminating in a meningitis. Neither capsular polysaccharide nor agglutinins were detectable in the blood, while precipitin was present in relatively high titer at the same time that the blood culture was positive.

(C) *Treatment with Serum and Sulfapyridine:* Table 3 summarizes the

TABLE III
Sulfapyridine Plus Serum

Sulfapyridine Plus Serum

Type	Patient	Age (yrs.)	Treatment						Sulfapyridine Concentration in Blood % Milligrams	Serum Titer †		
			Serum		Sulfapyridine		Capsular Poly-saccharide	Agglutinins		Precipitins		
			Day of Disease when Started	Quantity Units	Day of Disease when Started	Quantity Grams						
I	116433	37	6th	160,000§	6th	33	6.6 28.4	Negative	1:64	1:8		
I	116187	45	3d	110,000§	3d	53	3.9 7.0 7.8	Negative	1:64	1:8		
III	115518	46	2d	300,000	2d	23	3.9 8.9	Negative	1:32	1:4		
VII	116551	22	7th	232,500	7th	22	3.2 3.6	Negative	Note: Antibodies negative before treatment. No studies made after treatment			
VII*	115898†	47	12th	160,000	12th	29	24.2 6.6 6.0	Negative	1:64	1:16		
VII*	112875† (W.L.)	61	3d	2,525,000¶ (in three courses)	12th	242 (in three courses)	1st course 4.0 to 9.3 2d course 9.6 to 12.4 3d course 2.1 to 11.6	Positive	1:64	1:16		

* Bacteremia.

† Died.

‡ Highest titer.

§ Horse serum (all others rabbit serum).

¶ Horse and rabbit serum.

results obtained in six cases treated with serum and sulfapyridine. In one of these cases capsular polysaccharide was detectable in the blood. This patient, W. L., described in a previous communication¹³ as having recovered with combined therapy, subsequently died.

He was a 61-year old colored male with a severe pneumococcus VII pneumonia who developed an overwhelming bacteremia, despite antipneumococcal serum therapy. He had undergone apparent remission under further serum therapy, combined with sulfapyridine. His blood had then given a positive reaction for capsular polysaccharide, persisting for eight days, together with detectable homologous precipitin. Capsular polysaccharide had finally disappeared, as infection came under control. Following withdrawal of sulfapyridine, the elevation of temperature had recurred and capsular polysaccharide reappeared in the blood, together with detectable antibody. A second course of sulfapyridine, this time without serum, had promptly brought the temperature to normal and capsular polysaccharide had again disappeared from the blood.

The patient remained subjectively well without elevation of temperature or pulse for about two weeks following the second withdrawal of sulfapyridine. This was followed by gradual elevation of temperature to 101° F. Though there had been previous slight loss of antibody from the blood, capsular polysaccharide reappeared only after several days of elevated temperature. At this time the patient developed signs of meningeal irritation, a right lower motor neuron facial paralysis, right hemiparesis, and aphasia. The blood culture was again positive for pneumococcus VII. The cerebrospinal fluid contained numerous polymorphonuclear leukocytes but did not become positive for pneumococcus VII until the following day. He was promptly treated by careful administration of 700,000 units of antipneumococcal serum, and sulfapyridine again. Within four days the temperature had fallen to normal, blood and spinal fluid had become sterile, capsular polysaccharide had disappeared from the blood stream, and he had developed a high titer of circulating precipitins and agglutinins. During the next few days, his temperature remained normal and the meningeal and focal neurologic signs diminished in intensity. However, one week later, the temperature gradually rose again and the spinal fluid culture became positive and remained so, despite maintenance of a concentration of sulfapyridine in both the blood and spinal fluid in the neighborhood of 10 mg. per cent. The blood culture remained sterile, circulating capsular polysaccharide did not reappear, and the circulating antibody titer also remained high. However, the temperature continued to rise, he sank into a stupor, and finally died on the seventy-sixth day of hospitalization. Permission for postmortem examination was withheld.

The organism recovered from his spinal fluid at the time of his terminal escape from sulfapyridine therapy was studied by Dr. Edwin E. Osgood. It was found to be less susceptible to bacteriostasis by sulfapyridine than the first strain, isolated from the same patient earlier in his disease.

Capsular polysaccharide was not detectable in the blood of the remaining five patients. One of these, suffering from pneumococcus VII bacteremia, treated on the twelfth day of disease, died despite a high antibody titer, high sulfapyridine concentration, and sterilization of the blood. Postmortem examination revealed pneumonic consolidation of the left lower and right middle lobes. The four remaining patients recovered. Three of them had a high titer of agglutinins and precipitins immediately after serum therapy, and made uneventful recoveries. In the fourth recovered patient, where

both pneumococcus I and pneumococcus VII were present in the sputum, the blood was negative for antigen and antibody for both types; studies were not made after serum therapy.

COMMENT

Including the present series, there have now been a total of 16 reported cases of pneumococcal pneumonia in whose blood free capsular polysaccharide was detected.^{1, 2, 3} Fourteen of these 16 cases died, a mortality of 87.5 per cent. The blood of one of the survivors contained only traces of polysaccharide.¹ The pneumonias in four of our patients were due to pneumococcus type III, three with bacteremia and the fifth was due to pneumococcus VII also with bacteremia.

Among our cases there were 10 bacteremic patients, of whom four presented detectable circulating capsular polysaccharide simultaneously with the bacteremia. Two of these four patients lived long enough to permit repeated blood determinations. Capsular polysaccharide continued to be detectable in the blood for 8 days and 10 weeks respectively, following the disappearance of bacteria. Three of these four patients died. Two patients had received sulfapyridine alone and one serum and sulfapyridine. Of the six bacteremic patients in whose blood capsular polysaccharide was not detected, two died; one received serum and sulfapyridine and one serum alone. While these observations are in a series too small to be statistically significant, they nevertheless suggest that the occurrence of free polysaccharide in the blood stream implies a more serious prognosis than does bacteremia alone, and that sulfapyridine alone, or even with specific serum, may not cure such patients. However, one patient with capsular polysaccharide in the blood fell in the drug series and recovered under sulfapyridine therapy alone but after a stormy, protracted illness. Reasoning that capsular polysaccharide exerts its effect by the inhibition of defenses against the pneumococcus,^{4, 5, 6} we suggest that attempts should be made to "neutralize" capsular polysaccharide by the administration of antipneumococcal serum to those patients in whose blood the substance is circulating. Judging from our experience with W. L. it is suggested that we might have shortened the illness in our recovered patient had specific antipneumococcal serum been administered early in addition to sulfapyridine.

It is possible to determine the presence or absence of capsular polysaccharide in the serum within 1 hour of withdrawal of the blood by the use of the centrifuge,^{14, 15} which is at least 12 to 20 hours earlier than it is possible to detect bacteremia. Consequently, if capsular polysaccharide determinations are routinely made it will be possible to select cases with a serious prognosis much more quickly than has been possible heretofore. Accordingly, since it is our belief that such patients should receive optimum therapy as quickly as possible, specific antipneumococcal serum therapy as well as sulfapyridine therapy may be promptly instituted. It remains for further

observations to determine whether or not a greater reduction in mortality of pneumococcal pneumonias, or other pneumococcal infections, may be accomplished by the inclusion of this laboratory criterion as a guide to therapy.

Since capsular polysaccharide continued to be detected in the blood of our recovering patient, it would seem that the polysaccharide may not be toxic per se. The adverse effects of polysaccharide in human infections are probably dependent upon the simultaneous presence of multiplying pneumococci.^{4, 5, 6}

Observations on the antibody response of this series of patients under the various forms of therapy, where capsular polysaccharide is not present in the blood, seem less significant. In a certain number of our patients treated with sulfapyridine alone, cure was effected some time before antibody was detected. Finland, Spring and Lowell¹⁶ have also observed a number of cases of type III pneumonia which recovered although after treatment with sulfapyridine was discontinued, there was no evidence of the presence of type specific antibodies in the blood. Robertson, Graeser, Coggeshall and Harrison¹⁷ have presented an excellent review of the literature and additional observations on the recovery of untreated pneumococcal pneumonia patients in whose blood antibodies were not detected.

SUMMARY AND CONCLUSIONS

1. Repeated simultaneous determinations of capsular polysaccharide and type-specific antibody were made in the blood of 26 patients treated for pneumococcal lobar pneumonia. Twelve patients received only sulfapyridine; eight patients only serum; and six patients sulfapyridine and serum.

2. Free capsular polysaccharide was detected in the blood of five patients, four of whom died. In the one patient treated with serum and sulfapyridine, (W. L.), temporary remission of the disease occurred. He subsequently died from a meningitis, at which stage the pneumococcus isolated from his spinal fluid proved to be relatively resistant to sulfapyridine. One patient, treated with sulfapyridine alone, recovered after a protracted illness requiring several courses of the drug.

3. Ten of the 26 patients were bacteremic. In four of these capsular polysaccharide was detected in the blood; three of these patients died. In six, capsular polysaccharide was not detected; two of these patients died. Bacteremia plus circulating capsular polysaccharide apparently confers a more serious prognosis than does bacteremia alone. It is suggested, on clinical as well as experimental grounds, that, to shorten the illness and decrease mortality of such cases, both antipneumococcal serum and sulfapyridine be employed as the therapy of choice.

4. Capsular polysaccharide can be detected in the blood stream 12 to 20 hours earlier than bacteremia and can be routinely used as a criterion for prognosis and therapy.

5. Of the 21 patients without capsular polysaccharide in the blood, two died; one had a pneumococcus IV endocarditis and meningitis and had been

treated with serum. The other suffering from a single-lobed, pneumococcus VII pneumonia with bacteremia, treated on the twelfth day of disease, with sulfapyridine and serum, died though there was considerable antibody and an adequate sulfapyridine concentration in the blood.

6. Observations in one case suggest that, in some instances, recrudescences of fever following withdrawal of sulfapyridine are related to transient reinfections.

7. In one case, where three different types of pneumococci were present in the sputum, the infecting type was determined by detecting the specific soluble substance for this type alone in the patient's urine.

8. In only a majority of the recovered patients, who received sulfapyridine alone, were antibodies detected by precipitation or agglutination. Several patients recovered without antibodies in the blood and others died despite the presence of a high titer of antibodies (some of them with sulfapyridine concentrations in the blood between 2 and 6 mg. per cent).

BIBLIOGRAPHY

1. BLAKE, F. G.: Antigen-antibody balance in lobar pneumonia, *Arch. Int. Med.*, 1918, xxi, 779-790.
2. DOCHEZ, A. R., and AVERY, O. T.: *Proc. Soc. Exper. Biol. and Med.*, 1917, xiv, 126.
3. DOCHEZ, A. R., and AVERY, O. T.: The elaboration of specific soluble substance by pneumococcus during growth, *Jr. Exper. Med.*, 1917, xxvi, 477-493.
4. FELTON, L. D., and BAILEY, G. H.: Biologic significance of the soluble specific substances of pneumococci, *Jr. Infect. Dis.*, 1926, xxxviii, 131-144.
5. DOWNIE, A. W.: Specific capsular polysaccharide of pneumococcus Type I and immunity which it induces in mice, *Jr. Path. and Bact.*, 1937, xlv, 131-147.
6. SICKLES, G. M.: Further observations on effect of Type I pneumococcus culture broth on phagocytic action of Type I pneumococcus serum, *Jr. Immunol.*, 1927, xiv, 329-336.
7. COLE, R., and DOCHEZ, A. R.: Reports of studies of pneumonia, *Trans. Assoc. Am. Phys.*, 1913, xxviii, 606-616.
8. PARK, W. H., BULLOWA, J. G. M., and ROSENBLÜTH, M. B.: Treatment of lobar pneumonia with refined specific antibacterial serum, *Jr. Am. Med. Assoc.*, 1928, xci, 1503-1508.
9. Medical Research Council, *Lancet*, 1934, i, 290.
10. LORD, F. T., and HEFFRON, R.: Lobar pneumonia and serum therapy, 1936, The Commonwealth Fund, Oxford University Press.
11. BULLOWA, J. G. M.: The management of the pneumonias, 1937, Oxford University Press.
12. HEFFRON, R.: Pneumonia, 1939, The Commonwealth Fund, Oxford University Press.
13. BUKANTZ, S. C., BULLOWA, J. G. M., and DE GARA, P. F.: Detection of free polysaccharide in blood of pneumococcal pneumonia patients; prognosis and therapy, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 250-254.
14. DE GARA, P. F., BUKANTZ, S. C., and BULLOWA, J. G. M.: Pneumococcal capsular polysaccharide in urine; detection by precipitation and centrifugation, *Jr. Immunol.*, 1939, xxxvii, 305-320.
15. DE GARA, P. F.: Influence of centrifugation on agglutination of pneumococci, *Science*, 1939, xc, 378.
16. FINLAND, M., SPRING, W. C., JR., and LOWELL, F. C.: *Jr. Clin. Invest.*, 1939, xviii, 483.
17. ROBERTSON, O. H., GRAESER, J. B., COGGESHALL, L. T., and HARRISON, M. A.: Relation of circulating antipneumococcal immune substances to course of lobar pneumonia; acquired immune substances, *Jr. Clin. Invest.*, 1934, xiii, 633-647.

OBSERVATIONS ON THE ABSORPTION, EXCRETION AND DISTRIBUTION OF SULFANILAMIDE, SULFAPYRIDINE, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE*

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IN a previous paper,¹ Taylor and his associates reported the results of studies on the absorption and excretion of sulfanilamide and sulfapyridine after administration of a single dose by various routes. Special consideration was given in that paper to a glucose-sulfapyridine solution which was shown to be absorbed, excreted and distributed in the body in a manner radically different from that of either sulfapyridine or sulfanilamide. The present paper deals with a continuation of these studies with particular reference to sulfathiazole and sulfamethylthiazole. We include also the results of studies of (1) the absorption and urinary excretion of the sodium salts and acetyl derivatives after oral administration, and of the various compounds and their sodium salts after rectal administration, and (2) the concentrations of sulfanilamide, sulfapyridine and sulfathiazole in the body fluids and organs of patients who died during treatment with these drugs.

MATERIALS AND METHODS

The subjects were all adult males. Three were normal volunteers and the others were ward patients, most of whom were convalescing from mild infections. None had received sulfonamide therapy within a week of the time these studies were begun. Blood non-protein nitrogen and urinary phenolsulfonphthalein excretion were normal in each instance. The ages and weights are given in table 1. Some of the studies on the distribution of drugs between plasma and red blood cells were made on blood taken from patients under treatment for various infectious diseases.

During the studies on absorption and excretion, the subjects were on a regular "house" diet with a fluid intake maintained at 3 liters a day. A uniform dose of 5.0 grams was used in each experiment. The intravenous injections were all given in 500 ml. of physiological saline over a period of 1 hour. The subcutaneous injections were given in a liter of fluid over a period of 1½ hours; the sulfanilamide was given in saline and the sulfathiazole was prepared by adding the 5 grams of powdered drug to a liter of

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TABLE I
Maximum Blood and Urine Concentrations and Urinary Excretion of Sulfanilamide Compounds after Intravenous,
Subcutaneous and Oral Administration of a Single 5-gram Dose

Compound	Subject			Maximum Blood Concentration			Maximum Urine Concentration			Urinary Excretion							
				Hours After Administration	Mg. Per Cent	Period (hours after administration)	Volume (ml.)	Mg. Per Cent	Per Cent of Administered Drug Recovered*								
	No.	Age	Weight (kg.)						Free	Total	Free	Total	In 24 Hours	In 72 Hours	First 24 Hours	24-72 Hours	
																	Free
After Intravenous Injection																	
Sulfanilamide	1	43	69	0	11.7	13.4	1-2	430	56	70	46.9	84.2	38.5	76.0			
	2	39	70	0	11.1	11.1	1-2	310	124	174	75.6	93.7	42.6	66.2			
Sodium sulfapyridine	1			0	9.5	10.3	12-24	780	24	179	61.4	90.0	74.9	90.1			
	3	63	68	0	9.8	11.1	2-5	300	116	202	84.5	99.7	61.6	84.1			
	4	26	58	0	9.9	9.9	0-2	25	215	332	37.7	80.0	22.0	37.0			
Sodium sulfathiazole	5	64	66	0	14.5	14.5	2-5	75	263	332	67.2	80.3	30.6	40.0			
	6	31	94	0	12.0	12.1	1-2	275	224	242	85.7	91.0	12.0	24.6			
	7	45	69	1/2†	12.5	12.7	1-2 1/2	90	440	445	79.0	84.0	11.0	34.4			
Sodium sulfamethylthiazole	8	24	58	1/2†	9.8	10.1	1/2-2	40	146	146	50.3	62.0	16.0	46.9			
	8			1/2†	9.7	10.0	1/2-1	110	154	154	48.0	60.5	8.5	38.6			
	9	58	89	0	12.4	12.5	6-12	600	97	113	51.8	60.1	12.0	44.0			
After Subcutaneous Injection																	
Sulfanilamide	1			4 1/2	9.0	10.6	12-24	1160	44	110	61.6	99.2	47.0	67.4			
	2			4 1/2	7.1	8.0	12-24	1700	42	94	68.4	92.5	43.6	69.7			
Sulfathiazole*	8			1	6.9	6.9	1-2	50	523	529	73.1	76.0	2.4	25.3			
	7			1	6.4	6.5	2-5	100	827	827	82.6	89.3	3.6	21.0			

* For the sodium salts, the urinary excretion is corrected both for sodium and for water of crystallization.

† First blood sample.

TABLE I—Continued

Compound	Subject			Maximum Blood Concentration			Maximum Urine Concentration			Urinary Excretion				
				Hours After Administration	Weight (kg.)	No.	Period (hours after administration)	Volume (ml.)	Mg. Per Cent	Per Cent of Administered Drug Recovered*	Per Cent of Recovered Drug Conjugated			
	Free	Total	In 24 Hours									In 72 Hours	First 24 Hours	24-72 Hours
										Free	Total			
	After Oral Administration													
Sulfanilamide	1			5†	6.6	7.8	12-24	1050	39	99	50.3	78.6	46.8	71.8
	2			5†	4.9	6.5	6-12	1180	51	84	71.8	90.7	43.7	67.0
Sulfapyridine	1			5†	3.2	5.3	12-24	700	21	153	47.0	76.0	76.0	83.0
	2			5†	5.5	7.7	6-12	1190	45	118	78.0	93.0	67.0	88.5
	4			5†	5.7	7.0	6-12	1100	45	67	47.2	82.8	24.4	44.0
Sodium sulfapyridine	5			2	7.9	8.5	12-24	250	125	200	29.0	70.1	27.0	49.7
	9			3	5.9	6.4	3-8	350	82	97	36.5	71.2	19.3	49.2
	10	35	65	6	5.7	6.4	6-12	700	73	99	46.0	—	24.0	—
Sulfathiazole	6			2	7.3	7.8	2-3	275	224	242	77.0	85.0	15.0	15.4
	5			6	8.8	10.3	12-24	530	187	250	66.6	90.0	19.0	33.5
Sodium sulfathiazole	6			3	7.2	7.6	3-6	320	256	256	60.0	73.0	9.0	6.2
	7			3	9.5	10.4	2-3	100	322	339	65.0	80.0	4.0	60.0
	7			2	9.4	9.9	2-3	150	240	247	64.3	73.0	6.3	44.4
Sulfamethylthiazole	9			3	7.9	8.3	6-12	400	149	152	42.0	49.0	5.0	27.3
	11	27	61	3	8.1	8.2	1-3	35	406	455	66.0	72.0	7.0	26.0
	9			3	4.8	4.8	3-12	1000	65	82	22.9	34.3	24.0	44.5
Sodium sulfamethylthiazole	12	27	59	4	5.5	6.0	4-6	50	131	186	25.6	38.0	35.0	54.1
	13	29	80	3	3.3	3.3	3-6	225	59	62	14.3	23.8	20.6	43.4
	7			2	8.3	8.7	12-24	700	58	77	35.1	47.6	15.0	33.3
	9			6	5.8	6.3	2-6	490	61	71	29.0	53.0	8.6	31.6
	14	32	66	3†	5.3	6.0	3-6	520	58	62	33.0	40.5	30.7	58.3

5 per cent glucose in distilled water between 90 and 100° C.* Boiling was avoided after the sulfathiazole was added. The oral and rectal doses were dissolved or suspended in tap water, using 500 ml. for the former and 300 ml. for the latter. Each subject was given a soap and water enema a few hours before rectal administration of the drugs.

No untoward reactions, local or general, followed the subcutaneous or rectal doses of any of the drugs. Some nausea accompanied the oral administration in most instances and several of the subjects vomited at or shortly after the completion of the intravenous injections.

Blood samples (oxalated) were taken at frequent intervals during the first 12 hours and at 12- to 24-hour intervals thereafter. All urines were saved and, in almost all instances, urine was obtained at the same time as the blood. Collections were continued until the urine showed no measurable amounts of drug—usually 96 hours or longer. Since there was rarely any significant amount of drug excreted after 72 hours, however, the figures are plotted to that time. A further period of 24 hours or longer was allowed to elapse before commencing a second study on the same subject.

Determinations of free and conjugated drugs in body fluids were carried out by the method of Bratton and Marshall,² using the Klett-Summerson colorimeter with No. 540 filter. Bile was usually diluted 1:10 with distilled water, and a trichloroacetic acid filtrate prepared from this dilution. In some instances turbidity, which persisted after centrifugation and filtration, made these determinations impossible. For the assay of organs, wet tissue (about 5 grams) was weighed, finely divided, then ground with sand and extracted three times with boiling distilled water. The determinations were then carried out on the watery extracts as for blood.

For the determinations on feces, the total output for 24 hours or more was mixed with warm acetone, dried to a constant weight and thoroughly pulverized. Duplicate 1 gram samples of the powdered feces were then placed in Soxhlet thimbles and extracted thoroughly with acetone. Usually about 250 ml. of acetone and 16 hours or more of extraction were required to complete this process. The acetone extracts were then diluted 1:10 with distilled water and the determinations were made on 0.5 to 1.0 ml. amounts of this dilution treated in the same manner as blood filtrates. This part of the study was carried out by Miss Margaret A. Adams.

RESULTS

Blood Concentrations and Urinary Excretion after Intravenous, Subcutaneous and Oral Administration of a Single 5-gram Dose of Sulfonamide Compounds. The essential data are summarized in table 1 and in figures 1 to 4. Maximum blood levels were attained immediately after the intravenous injection and, with few exceptions, within two to three hours after the oral administration of all the drugs studied. Following subcutaneous

* Bactericidal tests indicated that this solution was highly active against the pneumococcus.

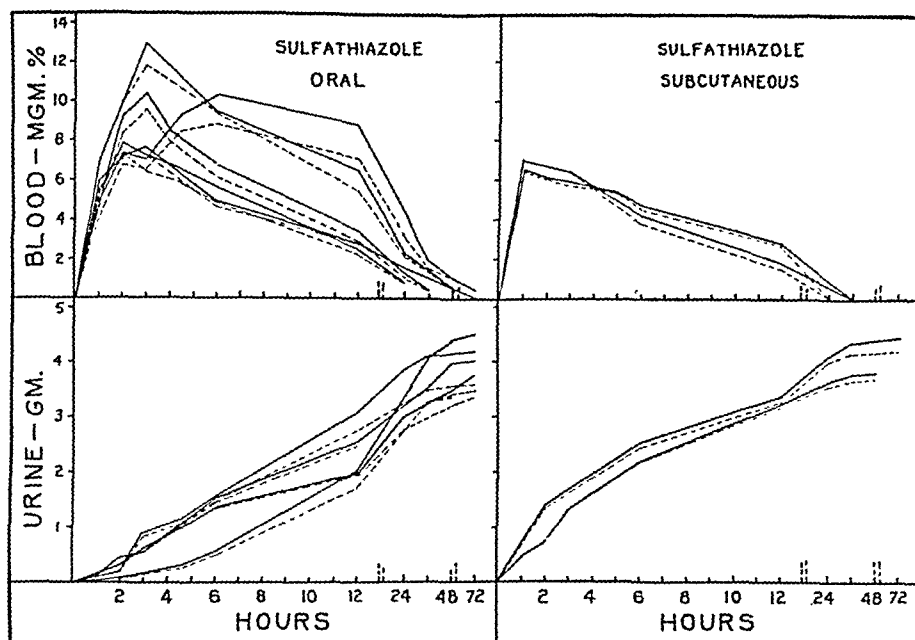


FIG. 1. Blood levels and cumulative urinary excretion of sulfathiazole after oral and subcutaneous administration of a single 5-gram dose in human subjects.

In figures 1 to 5 the solid line represents "total" drug and the dotted lines represent "free" drug. Each solid line and its corresponding dotted line are from one patient.

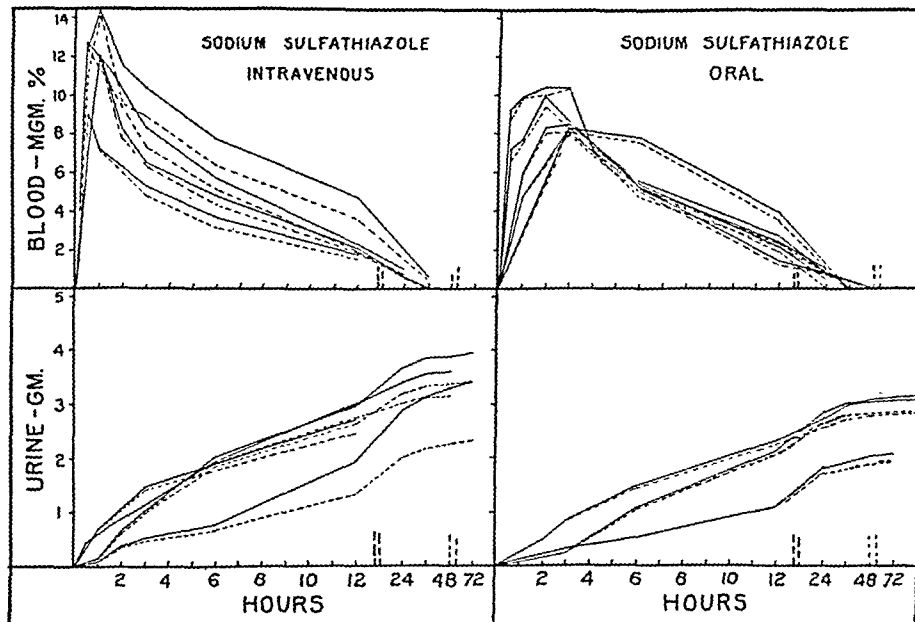


FIG. 2. Blood levels and cumulative urinary excretion of sodium sulfathiazole after intravenous and oral administration of a single 5-gram dose in human subjects.

administration, maximum levels of sulfathiazole in the blood were reached more promptly than in the case of sulfanilamide. With the latter, however,

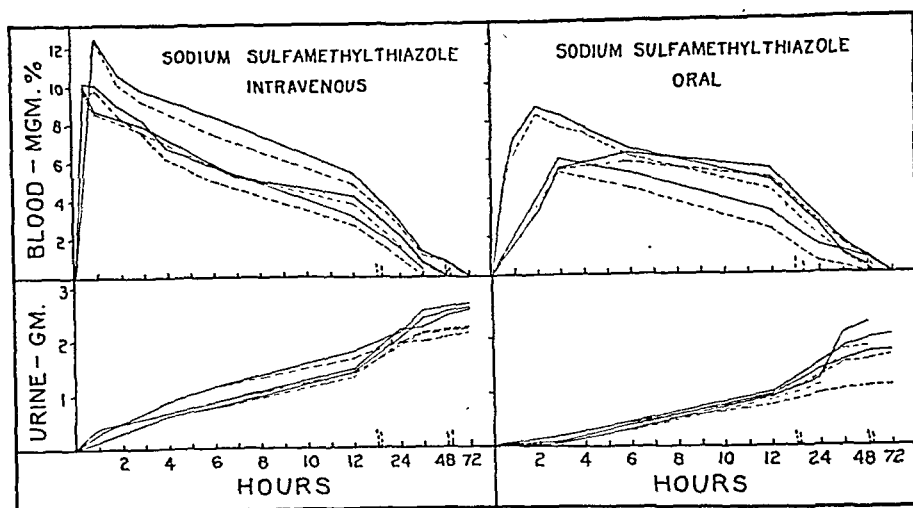


FIG. 3. Blood levels and cumulative urinary excretion of sodium sulfamethylthiazole after intravenous and oral administration of a single 5-gram dose in human subjects.

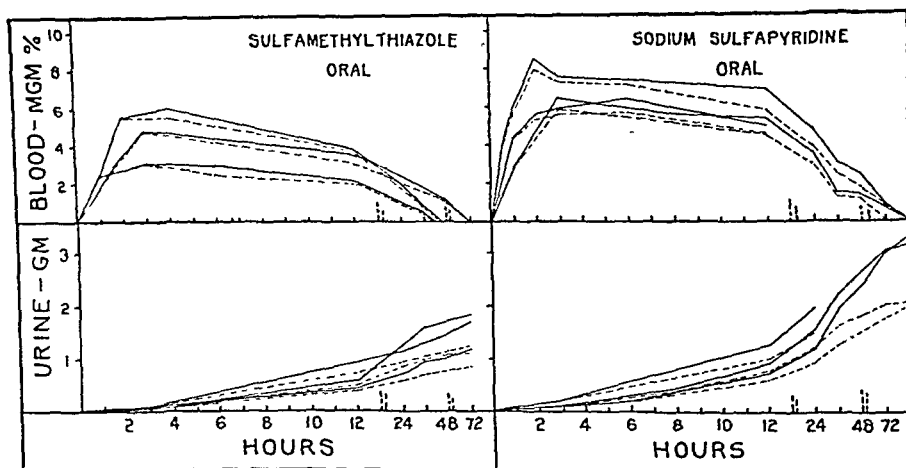


FIG. 4. Blood levels and cumulative urinary excretion after oral administration of a single 5-gram dose of sulfamethylthiazole and sodium sulfapyridine in human subjects.

the maximum blood levels were higher. Higher levels were obtained in the blood after intravenous and oral administration of the sodium salts than when the drugs themselves were given orally.* With similar doses, sodium sulfathiazole, given by mouth or by vein, yielded higher blood levels than any of the other compounds studied.

The relative amount of conjugated sulfathiazole and sulfamethylthiazole in the blood remained small regardless of the route of administration (figures 1 to 4). This is in sharp contrast to the percentage of acetylated sulfanilamide and sulfapyridine in the blood, which increases steadily with time.¹

* In the case of sulfapyridine, no blood samples were obtained for 5 hours after its oral administration so that the data do not permit this comparison.

The time of maximum urinary excretion varied with the drug given, with the route by which it was administered and also in individual subjects, but it always occurred within the first 24 hours. In most instances the maximum urinary excretion occurred soon after the maximum blood level was reached. As with the blood levels, sulfathiazole and its sodium salt showed the highest concentrations in the urine regardless of the route of administration, and the maximum excretion occurred earlier than with the other drugs.

The most complete recoveries of administered drugs were obtained following their intravenous and subcutaneous injections. Within the limits of the methods, the results indicated that, after parenteral injection, the elimination of sulfanilamide, sulfapyridine and sulfathiazole in the urine was essentially quantitative. This was not true of sulfamethylthiazole of which only 60 per cent appeared in the urine. Following oral administration, the amount of drug recovered from the urine averaged slightly less than after the parenteral injections.

The proportion of the total urinary excretion which occurred during the first 24 hours offers further comparisons. With sulfathiazole, about 90 per cent of the urinary excretion of the drug usually occurred within 24 hours (range: 70 to 95 per cent), whereas with the other drugs this proportion was usually about 70 per cent (range: 45 to 85 per cent). The route of administration had only a minor effect in this respect. The relative amounts excreted in this period were the same for each drug and for its sodium salt, except after the oral administration of sodium sulfapyridine. A smaller part of the excretion of the latter salt occurred in 24 hours, as compared with the amount excreted during the same period when sulfapyridine was given orally.

Most striking are the differences in the degree of conjugation of the various drugs found in the urine, particularly during the first 24 hours after their administration. The smallest percentage of conjugation in the urine was found with sulfathiazole, and the largest with sulfapyridine. With the former, the proportion of the drug recovered in the urine in conjugated form during the first 24 hours was sometimes as low as 2.4 per cent; with the latter it was as high as 76 per cent. Sulfamethylthiazole showed slightly more conjugation than sulfathiazole, and sulfanilamide somewhat less than sulfapyridine. In the case of each drug the percentage of the excreted drug which was conjugated was essentially the same regardless of the route of administration. Sodium sulfapyridine given by mouth appears to be an exception in that less of the excreted drug was acetylated than was the case after its intravenous injection or after the oral administration of sulfapyridine.

That individual subjects may vary with respect to the extent to which they conjugate these drugs is most clearly illustrated by Subject 4. Following the intravenous injection of sodium sulfapyridine and after the oral ad-

ministration of sulfapyridine, this subject's urines contained the same total amount of drug but less than half as much conjugated sulfapyridine as was found in any of the other subjects who received the same materials in a corresponding manner.

Blood Levels and Urinary Excretion after Rectal Administration of a Single 5-Gram Dose (Table 2 and Figure 5). Sulfanilamide was absorbed fairly rapidly following its rectal administration. The maximum levels were reached in the blood 3 or 4 hours after its administration and were somewhat lower than when the oral route was used. From 41 to 68 per cent of the administered drug was excreted in the urine, and from 40 to 48 per

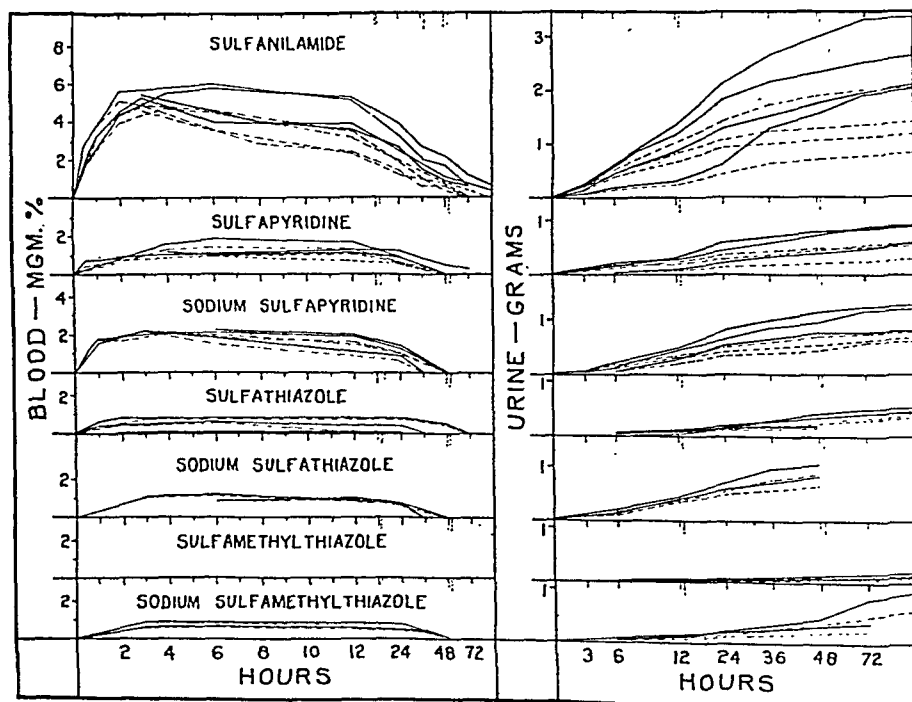


FIG. 5. Blood levels and cumulative urinary excretion after rectal administration of a single 5-gram dose of various sulfonamide compounds in human subjects.

cent of the drug recovered in the urine was acetylated. Most of the urinary excretion of the drug occurred in the first 48 hours, and less than 2 per cent of the total amount was recovered after 96 hours. Only 12 per cent of the administered drug was recovered from the feces of the 2 subjects in whom this was determined.

The other drugs were all poorly absorbed. The sodium salts were absorbed somewhat better than the corresponding drugs. Sulfapyridine was absorbed somewhat better than sulfathiazole so that the blood levels were higher and a larger percentage of the administered sulfapyridine was recovered from the urine.

TABLE II
Urinary Excretion and Maximum Blood Concentrations of Sulfonamide Compounds after Rectal Administration of a Single 5-Gram Dose

Compound	Subject	Maximum Blood Concentration	Hours After Administration	Mg. Per Cent	Free	Mg. of Drug Excreted in Urine	Total	First 24 Hours	Free	96 Hours	Total	Recovered from Feces	Hours After Administration	Mg. 11	Second Stool	Per Cent of Administered Drug Recovered from	Urine*	Feces*

See also figure 5.

* The percentage of the sodium salts excreted is corrected both for sodium and for water of crystallization.

† First blood taken.

‡ Done by water extraction.

§ No drug found in urine or stool after 48 hours.

|| Total drug.

In most instances where determinations were made on the feces, it was possible to recover a large proportion of the administered drug in the first stool passed. Regardless of the amount recovered from the first stool and the time when it was passed, however, only very small additional amounts were recovered from subsequent stools. Almost all of the drugs recovered from the feces were in the unconjugated form. The total amounts recovered from both urine and feces varied widely. In some instances as much as three-fourths of the administered drug was recovered from the feces 24 hours after it was given.

Blood Levels and Urinary Excretion after Administration of 5 Grams of the Acetyl Derivatives of 3 Sulfonamide Compounds. The results of the few studies made with acetyl compounds are shown in table 3. Only acetylsulfanilamide was absorbed to any considerable extent. Even with this drug, the maximum blood level attained was lower and the total amount of drug recovered from the urine was less than after the ingestion of sulfanilamide. The maximum blood levels after the oral administration of acetylsulfapyridine were only 2.1 and 2.4 mg. per 100 ml., and only from 20 to 32 per cent of the administered drug was recovered from the urine. The highest blood level in the subject who received acetylsulfathiazole orally was 0.7 mg. per 100 ml., and he excreted into his urine a total of 7 per cent of the ingested drug. The percentage of drug found in the blood and urine in the unconjugated form was always small. In the one subject who received the acetylsulfathiazole, the small amount recovered from his urine showed a considerably greater unconjugated portion than was found in any of the subjects who received acetylsulfanilamide or acetylsulfapyridine. One subject given acetylsulfapyridine directly into the duodenum (as verified by fluoroscopy) likewise showed very little absorption into the blood or excretion into the urine.

Distribution of Sulfonamide Compounds between Blood Plasma and Red Blood Cells. This was studied for the "free" drugs and the data are shown in table 4. Sulfanilamide was found in higher concentrations in the cells than in the plasma. For this drug, the ratio of the concentration of the drug in the cells to that found in the plasma was about 10 to 7. Sulfapyridine, however, occurred in slightly greater concentration in the plasma than in the red blood cells. If the concentrations are expressed in terms of the water content of the cells and of the plasma, however, they are practically equal.*

The distribution of sulfathiazole and sulfamethylthiazole, however, is different. The distribution ratio for sulfathiazole, except after its subcutaneous administration, varied from 1.4 to 2.6. In general, the ratio of

* Some of the data concerning sulfanilamide and sulfapyridine are taken from the previous study.¹ The actual water contents were not determined. However, if one assumes values of 0.64 and 0.91 per cent for the water content of cells and plasma, respectively, the ratio of the concentration in plasma water to that in cell water would be 0.7 times P/C (table 4). These values were also assumed in the calculation of renal clearances.

TABLE III
Blood Concentrations and Urinary Excretions after Administration of a Single 5-Gram Dose
of the (Para-) Acetyl Derivative of 3 Sulfonamide Compounds

Compound and Route of Administration	Subject	Hours after Administration	Blood		Urinary Excretion						Per Cent of Administered Drug Excreted	Per Cent of Excreted Drug Unconjugated
			Mg. Per Cent		Volume (ml.)	Mg. Per Cent		Amount (mg.) Cumulative				
			Free	Total		Free	Total	Free	Total			
Acetylsulfanilamide (Oral)	9	1	0.4	3.4	80	4	48	3	38			
		3	0.6	6.4	120	14	132	20	204			
		6	0.6	5.4	140	22	220	51	512			
		12	0.6	4.2	380	19	86	122	838			
		24	0.3	2.3	1400	12	75	283	1885		15	
		36	T	1.6	1900	8	38	429	2603			
		48	T	1.2	950	7	33	491	2918	44		
		72	0	0.1	2200	3	9	548	3109	72	18	
Acetylsulfapyridine (Oral)	6	1	0.0	0.3	60	1.4	9.4	1	6			
		2	0.3	1.2	230	1.6	4.7	5	17			
		3	0.3	1.2	280	2.2	4.7	11	30			
		6	0.4	2.4	1000	3.1	24	42	271			
		12	0.7	2.2	1000	2.7	65	69	921			
		24	0.4	0.5	900	16	81	83	994			
		36	0.4	0.4	1400	3.4	9.2	130	1123	23	8	
		48	0.6	0.9	600	2.7	7.1	146	1165			
		72	0.0	0.0	1700	1.6	9.3	174	1324			
		96	0.0	0.0	2400	0.6	1.3	188	1355	32	14	

TABLE III—Continued

Compound and Route of Administration	Subject	Hours After Administration	Blood		Urinary Excretion				Per Cent of Administered Drug Excreted	Per Cent of Excreted Drug Unconjugated					
			Mg. Per Cent		Volume (ml.)	Mg. Per Cent		Amount (mg.) Cumulative							
			Free	Total		Free	Total	Free			Total				
Acetylsulfapyridine (Oral)	12	1	0.0	0.8	300	0.0	1.6	0	5	14	12				
		2	0.6	1.8	200	1.0	16.3	2	38						
		3	0.6	2.1	300	1.6	18.4	7	93						
		6	0.8	1.5	300	5.2	66.3	23	292						
		12	0.6	0.7	800	2.8	21.4	45	463						
		24	0.6	0.5	675	3.6	17.1	69	578						
		48	T	T	2700	1.2	4.5	101	700						
		72	0.0	0.0	2600	1.5	3.5	140	791						
		96	—	—	3100	0.7	1.9	162	850						
Acetylsulfapyridine (Duodenal)	12	1	0	0.6	400	0	1.1	0	4	6	19				
		1	0	0.7	140	0.8	6.0	11	13						
		2	0	0.8	220	2.7	8.4	17	31						
		3	0	0.7	115	1.2	14.2	19	48						
		6	0	0.8	800	0.7	8.6	25	116						
		12	0	0.3	300	3.2	19.5	34	175						
		24	0	T	820	1.9	10.8	50	264						
		36	0	0	2200	0.7	3.8	65	247						
		48	0	0	825	1.8	6.9	80	404						
Acetylsulfathiazole (Oral)	7	1	0	T	210	1.4	2.8	3	6	6	37				
		3	T	T	440	1.4	5.8	9	31						
		6	T	0.7	300	6.3	23.0	28	102						
		12	0	T	1250	3.0	8.6	66	209						
		24	0	T	1700	2.0	3.5	100	269						
		36	0	0	1900	0.7	1.1	113	290						
		48	0	0	1800	0.7	0.7	125	302						
														7	41

T = trace.

TABLE IV
Distribution of Sulfonamide Compounds (Unconjugated) between Blood Plasma
and Red Blood Cells

Compound	Subject	Route of Administration	Time After Drug Given or Added	Concentration (mg./100 ml.)			$\frac{P}{C}$	Hematocrit (corrected)
				Whole Blood	Plasma (P)	Cells (C) (calculated)		
Sulfanilamide	13	*	10 minutes	8.5	7.6	9.4	0.8	50.2
			3 hours	9.7	7.4	12.0	0.6	50.2
	15	*	10 minutes	9.7	7.7	11.9	0.6	46.9
			3 hours	9.3	7.5	11.3	0.7	46.9
Sulfapyridine	16	Oral	†	4.6	4.7	4.4	1.1	33.0
	17	Oral	†	9.5	10.4	8.2	1.3	39.0
	18	Oral	†	19.0	19.2	18.7	1.0	40.0
Sodium sulfapyridine	7	Venous	30 minutes	6.8	7.5	5.7	1.3	42.0
	13	*	10 minutes	8.1	8.7	7.6	1.1	50.2
			1 hour	8.1	8.8	7.4	1.2	50.2
	15	*	10 minutes	8.3	8.7	8.0	1.1	46.9
			3 hours	8.2	8.6	7.7	1.1	46.9
Sulfathiazole	7	Subcutaneous	3 hours	6.2	9.2	1.9	4.8	40.9
			5 hours	5.4	7.8	2.1	3.7	41.8
	8	Subcutaneous	2 hours	7.3	11.2	2.8	4.0	45.8
	17	Oral	†	2.3	2.7	1.5	1.8	45.2
Sodium sulfathiazole	11	Oral	3 hours	8.1	11.0	4.2	2.6	43.4
	7 18	Venous Venous	30 minutes	12.6	16.3	7.7	2.1	43.0
			1 minute	26.0	28.5	17.3	1.6	22.0
			30 minutes	13.7	15.1	8.6	1.8	22.0
	6	Venous	1 hour	12.0	13.8	9.5	1.5	43.0
			3 hours	6.3	7.6	4.7	1.6	43.0
	5	Venous	50 minutes	14.5	16.1	11.4	1.4	33.4
Sulfamethylthiazole	7	Oral	1 hour	1.9	2.9	0.5	5.8	43.1
			3 hours	4.0	6.0	1.0	6.0	40.1
	19	Oral	2 hours	2.0	3.4	0.4	8.5	46.0
Sodium sulfamethylthiazole	9	Venous	1 hour	12.4	20.4	1.9	10.7	43.0
			3 hours	9.2	15.2	1.5	10.1	44.7
	20	Venous	2½ hours	13.2	19.2	5.5	3.5	43.9

* Added in vitro.

† Patient under treatment.

the concentration of sulfathiazole in the plasma to that in the red blood cells was about 1.8 to 1, or about 1.3 to 1 on the basis of water content. After

subcutaneous administration of this drug the ratio was higher. The possible significance of this finding will be discussed later.

Sulfamethylthiazole penetrated the red blood cells even less than sulfathiazole. The concentration of this drug in the cells was only one-third to one-tenth of that found in the plasma.

Renal Clearances of Sulfathiazole and Sulfamethylthiazole and Their Distribution in the Body. The clearances for sulfanilamide and sulfapyridine as previously given¹ indicated considerable degrees of tubular reabsorption which varied a great deal in individual subjects. The data for sulfathiazole (table 5) indicate that, in general, there was less tubular reabsorption of this drug than of either sulfanilamide or sulfapyridine. Furthermore, the rate at which the blood was cleared of sulfathiazole was more uniform in different subjects than was the case with the other two drugs. On the other hand, sulfamethylthiazole or its sodium salt was cleared from the blood at a much lower rate, indicating a considerably greater degree of tubular reabsorption. The estimations were made on "total" (free and conjugated) drug,* since the amount of conjugated drug in the blood was always small.

It was also estimated from the available data that sulfathiazole was apparently distributed in a portion of the body considerably in excess of the extracellular water but less than the total body water. Sulfamethylthiazole gave variable results in different subjects. In two individuals (Numbers 9 and 20) the data suggested that the drug was confined essentially to the extracellular water, while in a third subject (Number 8) data obtained on two separate occasions suggested that the drug was distributed throughout most of the body water. Possible explanations of the latter differences will be discussed later.

Concentration of Drugs in Body Fluids and Organs of Patients Who Died while Under Treatment (Table 6). Most of the studies were done on patients who died within a few hours of the time the last dose of drug was given. In five of the sulfapyridine treated cases, no drug had been given for 16 hours or more before the time of death. The concentration of the drugs in the blood obtained from the heart varied considerably, as did the percentages of the drugs that were conjugated. In general, the patients who had high blood non-protein nitrogen levels before death also had, at autopsy, high concentrations of drug in the blood with large proportions of it in conjugated form. The sulfathiazole treated cases had the lowest percentage of conjugation in the blood. Since there were considerable variations among the findings in different patients, only the general trends of the findings in the fluids and organs in relation to the blood concentrations will be mentioned.

In the spinal fluids, the levels were generally lower than in the blood. Sulfathiazole showed the greatest and most constant difference in this respect, the spinal fluid levels all being about one-third of those found in the

* Distributions of "total" drug between serum and cells were used for this purpose.

TABLE V
Renal Clearances of Sulfathiazole and Sulfamethylthiazole
after Administration by Various Routes

Compound	Route	Subject	Length of Period (minutes)	Average Serum Concentration for Period (mg./100 ml.)*	Total Drug Excreted in the Period (mg.)*	Blood Cleared (ml. per minute)	Apparent Distribution (per cent of body weight)	
Sulfathiazole	Oral	6	180	7.0	667	53		
		6†	180	7.2	819	63		
			360	4.3	596	38		
		7	120	8.5	684	67		
	360		5.7	995	49			
	5	360	9.5	1437	40			
		Subcutaneous	7	240	7.5	1137	63	
			360	5.1	832	45		
Sodium sulfathiazole		Oral	7	180	7.2	668	52	
	360			4.3	834	54		
	9		360	5.3	607	32		
			11	180	10.7	833	45	
	360	7.4		1054	40			
	Intravenous	5	360	6.1	1133	51	42	
		6	180	6.4	958	83		
			360	4.0	962	67	38	
7		180	8.3	757	51			
360	4.7	1084	64	38				
Sulfamethylthiazole	Oral	9	540	6.6	816	25		
		720	4.8	230	7			
	13	180	5.2	144	15			
		360	4.2	216	14			
Sodium sulfamethylthiazole	Oral	7	180	10.8	231	12		
		360	8.4	533	18			
		9	360	8.9	554	17		
		14	180	8.8	322	20		
	360		6.3	506	22			
	Intravenous	8	120	8.3	295	29	69	
		360	5.8	632	30			
		8†	300	6.4	435	23		
			720	4.3	627	20	55	
		9	180	14.6	297	11		
360			12.8	678	15	22		
20‡	140	19.3	582	25	31			

* Sulfathiazole or sulfamethylthiazole.

† Separate experiment on same subject.

‡ Age 14 years, weight 45 Kg.

TABLE VI
Concentration of Sulfanilamide, Sulfapyridine and Sulfathiazole in Body Fluids and Organs
of Patients Dying While Under Treatment with These Drugs

Case	Sex	Age	Diagnosis	Days of Drug Therapy	Total Dose (gm.)	Hours from Last Dose to Death	Hours from Death to Autopsy	Ante-mortem Blood Non-Protein Nitrogen* (mg. %)	Concentration in Body Fluids (mg. per 100 ml.)						Concentration in Organs (mg. per 100 gm. of tissue)							
									Heart's Blood		Cerebro-Spinal Fluid		Bile		Bladder Urine	Kidney	Liver		Lung		Spleen	Brain
									F	T	F	T	F	T			F	T	F	T		
Sulfanilamide Treated Cases																						
1	M	33	Erysipelas; alcoholism	4	12	3	9	29	4.3	8.1	3.3	4.4	16.0	26.0	63.6	206.6	4.2	7.5	5.0	3.1	5.1	
2	M	70	Erysipelas; septicemia	4	22	8	18	29	10.1	17.5	7.9	9.5	—	—	38.9	100.1	15.5	16.5	14.7	18.1	10.5	
3	M	39	Staph. aureus meningitis	2	8	4	14	40	4.7	7.0	—	—	—	—	11.2	23.2	4.0	5.2	3.8	4.7	5.3	
4	M	1	Influenzal meningitis	3	14	7	6	26	—	—	—	—	—	—	—	—	18.8	23.2	20.7	21.7	19.8	
Sulfapyridine Treated Cases																						
5	F	52	Pneumococcal meningitis	6	33	33†	19	39-119	15.3	41.2	6.4	14.7	8.0	17.7	53.6	225.1	36.5	58.0†	18.5	20.6	10.8	
6	F	9/12	Influenzal meningitis	5	8	8	16	—	4.1	5.7	3.6	4.7	6.4	8.9	—	—	8.5	10.5	—	—	4.7	
7	M	3/12	Staph. aureus sepsis	3	5	6	19	—	21.5	23.7	16.2	16.7	30.2	31.8	—	—	22.3	22.3	18.5	18.5	18.5	
8	M	60	Strep. fecalis endocarditis	4	12	9	12	89	7.2	9.5	—	—	—	—	48.3	82.9	14.5	19.1	5.0	5.8	5.3	
9	M	71	Pneumonia; endocarditis	7	41	18	3	59-80	4.4§	17.8§	1.9	5.3	—	—	32.0	200.0	9.3	28.9	3.9	8.4	3.4	
10	F	41	Pneumococcal meningitis	6	33	16	96	25-41	11.8	13.3	10.0	10.0	—	—	—	—	31.0	36.0	15.0	16.0	15.0	
11	M	70	Pneumococcal meningitis	1	8	6	13	31	13.9	15.3	11.8	12.5	—	—	—	—	47.0	49.0	21.0	22.0	22.0	
12	M	51	Pneumococcal meningitis	3	31	35	7	27-115	23.4	28.4	13.8	16.0	—	—	89.4	109.0	43.6	50.8	26.4	30.4	30.4	
13	F	53	Lobar pneumonia	5	30	5	10	31	11.3	13.3	—	—	—	—	104.0	154.0	23.2	26.0	14.9	15.8	15.8	
14	M	80	Lobar pneumonia	7	22	96	2	60-140-75	Trace	1.8	—	—	—	—	24.8	49.8	2.6	4.9	Trace	1.9	—	
15	M	41	Pneumonia; meningitis	18	69	3	22	32	6.0	10.5	4.3	5.7	—	—	151.0	254.0	20.4	30.6	7.5	8.9	—	
Sulfathiazole Treated Cases																						
16	M	65	Lobar pneumonia	2	9	7	7	43	5.0§	7.3§	1.5	1.9	9.3	9.8	55.5	76.7	17.1	20.2	7.3	7.7	4.6	
17	F	63	Lobar pneumonia	12	52	6	4	53	3.3	4.0	1.2	1.4	—	—	219.6	254.4	11.3	15.5	2.5	2.5	3.6	
18	M	48	Lobar pneumonia	7	40	12	3	55-67-34	1.7	2.1	—	—	3.4	5.8	118.1	178.6	3.9	5.1	3.1	3.9	1.5	
19	M	68	Miliary tuberculosis	18	76	12	7	44-75-56	11.8	16.5	3.5	6.0	—	—	27.7	70.0	19.0	27.0	13.0	14.7	10.7	
																		4.3	5.1	6.7	—	—
																		2.2	3.6	2.2	—	—
																		10.9	13.1	—	—	—

F = free. T = total.

* The first and last determinations are given. When the levels rose and subsequently declined, the highest level is also given.

† Drug stopped because of hematuria and oliguria.

‡ Medullary portion 36.1 and 71.7 mg. per cent free and total, respectively. Bloody material in kidney pelvis 153 and 388 mg. per cent free and total, respectively.

§ Clotted—determination made on serum.

|| Consolidated portion used in pneumonia cases.

blood. Sulfanilamide and sulfapyridine showed wide variations, the spinal fluid levels ranging from one-third to four-fifths of blood levels. The proportion of drug in the conjugated form was essentially the same in spinal fluid and blood with sulfapyridine and sulfathiazole, but was lower in the spinal fluid with sulfanilamide.

The bile contained the drugs in higher concentration than the blood, but the proportion of the free and conjugated forms was essentially the same. In Case 5 there was less sulfapyridine in the bile than in the blood, but there were other similar discrepancies in this case.

The bladder urine contained high concentrations of drug in each instance, the levels ranging from 3 to more than 50 times the concentrations in the blood. In most cases, from one-half to four-fifths of the sulfanilamide and sulfapyridine in the urine was conjugated, whereas two-thirds or more of the sulfathiazole in the urine was in the "free" form.

With respect to the concentration of the drugs in the kidney, there was a striking difference between sulfanilamide, on the one hand, and sulfapyridine and sulfathiazole, on the other. Sulfanilamide was found in the kidney in concentrations which were essentially the same as in the blood and not very different from those found in the other organs. Sulfapyridine and sulfathiazole were usually present in the kidney in two or more times the concentration found in the blood or in any of the other organs (Case 7 is the only exception). When samples of medulla and cortex were studied separately, the former sometimes showed a slightly higher concentration than the latter, particularly of the acetylated drug (cf. Case 5).

In the liver, more than half of the cases showed more "free" drug than was found in the blood or in the other organs (except the kidney). However, the amount and percentage of conjugated drug in the liver were lower in almost every instance. The latter difference was most striking when the blood contained a high concentration of conjugated drug. The findings in the liver were similar for each of the three drugs.

In the lung and spleen, the concentrations of the drugs were essentially the same or slightly lower than in the blood. In the brain, however, the drugs were usually present in much lower concentrations than in the other organs.

DISCUSSION

The results of the studies on the absorption and excretion of sulfanilamide and sulfapyridine are essentially in accord with those of other workers.^{3, 4, 5} The only new feature brought out here concerns the oral administration of sodium sulfapyridine. In the three subjects presented here and in a limited number of observations made on patients, the degree of acetylation, both in the blood and in the urine, was regularly less when the sodium salt was given by mouth than when sulfapyridine itself was used in the same manner. No other differences were noted. In view of the prob-

able importance of the acetylsulfapyridine in the causation of renal complications,^{6, 7, 8} this may be of some clinical significance.

Many of the findings concerning the absorption and excretion of sulfathiazole have already been noted by other workers, both in animals^{9, 10} and in man.^{11, 12} Sulfathiazole was found to differ from both sulfanilamide and sulfapyridine in three important respects: (1) It was absorbed more rapidly after its oral administration and gave higher levels earlier. (2) It was excreted more rapidly into the urine, the maximum excretion occurring earlier and a larger proportion of the ingested drug being recovered during the first 24 hours. (3) A smaller percentage of the drug found both in the blood and in the urine was in the conjugated form. The latter is probably dependent, in part at least, on the rapidity with which the drug is eliminated. That portion of the drug which is excreted after the first 24 hours is conjugated to a considerable degree.

Our observations indicated that sulfamethylthiazole and its sodium salt were not absorbed as well as the other drugs, and a smaller proportion of the administered drug was recovered from the urine. This was true regardless of the route of administration. The methyl compound was acetylated to a considerably greater extent than sulfathiazole. This is significant because the methyl compound and its acetyl derivative are both much less soluble than sulfathiazole and its acetylated form.

The studies concerning the rectal administration of the various drugs are of interest in view of some apparently conflicting reports.^{11, 13, 14, 15} Our findings suggest that, of the compounds studied, only sulfanilamide is absorbed to any extent sufficient to warrant its use by this route clinically. The only other drug which was absorbed to any appreciable extent was sodium sulfapyridine, but even with this compound the low levels attained in the blood, the small percentage of administered drug recovered from the urine and the large amount found in the feces after 24 hours or longer indicate that it should not be recommended for use by the rectal route. The reported successes with its use may be related possibly to differences in absorption between infants and adults or to the use of larger doses or different methods of administering them.

The acetyl derivatives were all poorly absorbed. Observations in this laboratory and those of other workers have indicated that these derivatives are essentially devoid of antibacterial activity. From the results shown in table 3, it appears that these compounds are not deacetylated in the body to any appreciable degree after their oral or duodenal administration. Furthermore, in the few observations made, nausea and vomiting were certainly not less than with the parent compounds. These findings are of particular interest in view of the Danish report of the successful clinical use of acetylsulfapyridine in the treatment of pneumonia.¹⁶

In the previous study¹ it was shown that when glucose-sulfapyridine was added to human blood *in vitro* or administered parenterally, the sulfapyridine

was found almost entirely in the plasma. This was in sharp contrast to sulfanilamide, which was found in somewhat greater concentration in the red blood cells than in the plasma, and sulfapyridine, which was about equally distributed. From the present findings, it appears that the four drugs studied all varied with respect to their distribution between plasma and red blood cells. The drugs arranged themselves in this respect in the following order: (1) sulfanilamide, which, as already noted and as shown by others,^{17, 18} occurred in greater concentration in the cells than in the plasma; (2) sulfapyridine, which occurred in somewhat greater concentration in the plasma but was about equally distributed between plasma and red cells on the basis of their water content (cf. also¹⁸); (3) sulfathiazole, of which the concentration in the plasma was definitely greater than that in the cells; and (4) sulfamethylthiazole, which penetrated the red blood cells even less than sulfathiazole. The findings were essentially the same with the various compounds, with their sodium salts and with the different routes of administration, except in the case of sulfathiazole. When this drug was given subcutaneously it appeared to penetrate the red blood cells less than after its administration by other routes. This may be due to the fact that, in order to affect the solution of sulfathiazole in the desired concentration, it was added to hot 5 per cent glucose solution. The possibility that part of the drug was combined with the glucose during this process cannot be excluded, even though the resulting solution apparently retained its bactericidal activity. The resulting glucose-sulfathiazole may then have failed to penetrate the red blood cells, as was the case with the corresponding sulfapyridine solution.

The rate of renal clearance of sulfathiazole was somewhat higher than that of sulfanilamide and sulfapyridine, but it still indicated a fair amount of tubular reabsorption. On the other hand, sulfamethylthiazole and its sodium salt were cleared from the blood at a very low rate, which probably indicated considerable reabsorption from the glomerular filtrate.

The apparent distribution of sulfathiazole in the body fluids was in a volume of water somewhat greater than the extracellular fluid, but considerably less than the total body water. This finding is consistent with the poor penetration of this compound into the red blood cells and with the low concentrations of the drug found in the cerebrospinal fluid.

The data concerning the apparent distribution of sulfamethylthiazole are somewhat confusing. In two subjects the values suggested that the drug was essentially confined to the extracellular water, which is consistent with the findings already noted concerning the lack of penetration of this compound into the red blood cells. In the third subject, however, the data indicated a distribution throughout almost the total body water. There are some reasons to suspect that calculations based on the data concerning distribution of sulfamethylthiazole may not be satisfactory. The fact that only 60 per cent of the administered drug was recovered from the urine raises the question of whether a true estimate of the amount of drug available for

distribution can be made except in the very early period after its administration. Also, the drug, because of its insolubility, may be deposited, in part, in the bowel, and the concentration in plasma water would then not be representative of the concentration throughout the body water. Finally, the presence of large amounts of sulfamethylthiazole in the urine during certain periods may lead to crystallization of this drug at some stage of its determination. The evidence from the distribution between red blood cells and plasma is probably a more reliable index of what happens to this drug in the body than the calculation based on urinary excretion and serum water calculations.

Animal experiments have indicated that sulfanilamide is evenly distributed in the various tissues,¹⁹ while sulfapyridine is distributed somewhat unevenly.²⁰ In dogs sacrificed 4 hours after the administration of sulfapyridine, Marshall and Litchfield²¹ found the concentration of the drug to be higher in the liver than in the blood and other organs, but the kidney was not analyzed. In patients who died while under treatment with sulfapyridine, Brown et al.⁵ found the concentration of drug high in the kidney, but their data showed a higher level in the lung in one case.

In our cases, death occurred three or more hours after the last dose of drug was given. Large amounts of the drugs were retained in the tissues for many hours. In two cases, very high levels were found after 33 and 35 hours, and in one case measurable amounts were detected although death occurred 96 hours after the last dose of drug had been given. A variable interval elapsed between death and the time the tissues were obtained for analysis, but the effect of this factor cannot be evaluated.

The concentration of sulfapyridine and of sulfathiazole was consistently found to be two or more times as high in the kidneys as in the other tissues. Sulfanilamide behaved differently in this respect, its concentration in the kidney being the same as in the other tissues. While nitrogen retention was associated with retention of the drugs in all tissues, this factor did not account for the specific retention of sulfapyridine and sulfathiazole in the kidneys. The concentration in this organ was significantly higher than in the other organs, regardless of whether or not there was retention of nitrogen or drug. Contamination with urine likewise fails to explain the higher levels in the kidney, since this factor was equally operative in the case of sulfanilamide.

Bettman and Spier²² found higher levels in the bile than in the blood in patients with normally functioning gall-bladders. Our results indicate that this is also true for sulfapyridine and sulfathiazole. Under appropriate conditions it seems likely that these three drugs can be concentrated in the gall-bladder.

With all three drugs, the conjugated form was found in lower concentration in the liver than in the blood or in the other organs studied. This was more evident when the proportion of conjugated drug in the blood was

high. The concentrations of the unconjugated drugs, however, were frequently higher even when less conjugated drug was found. These findings are not entirely consistent with the concept that the liver is the site of acetylation of the sulfonamide drugs in humans, as was shown to be the case for sulfanilamide in rabbits.²³ However, we are not aware of any direct proof that the liver is the site of acetylation in humans.

The levels of sulfathiazole and sulfapyridine and, to a lesser extent, of sulfanilamide tended to be lower in the brain than in the blood. In the spinal fluid, however, the levels of sulfathiazole were consistently about one-third of those in the blood, while the concentrations of sulfapyridine and sulfanilamide, though variable, were frequently two-thirds or three-fourths of the blood levels. Our clinical experience also indicated that there was very little penetration of this drug into the spinal fluid even with moderately high blood levels, and Carey²⁴ has recently reported similar findings. From the point of view of therapy, these findings would suggest that sulfathiazole is not so desirable as the other drugs in the treatment of central nervous system infections.

SUMMARY

Data are presented concerning the blood concentrations and urinary excretion of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole and of the sodium salts of the latter three drugs after the administration to human subjects of a single 5-gram dose by various routes.

In general, the sodium salts given intravenously or orally yielded higher blood levels and these levels were attained more rapidly than when the corresponding drugs were given by mouth. The highest levels were obtained with sodium sulfathiazole.

Sulfathiazole and its sodium salt were excreted more rapidly into the urine than either sulfanilamide or sulfapyridine. All the drugs, with the exception of sulfamethylthiazole, were excreted more or less quantitatively after intravenous or subcutaneous injection, and almost all of the administered drugs were recovered from the urine after their oral administration. Only about 60 per cent of administered sulfamethylthiazole was recovered from the urine, regardless of the route by which it was given.

Sulfathiazole showed the least amount of conjugation and sulfapyridine showed the most. After oral administration of sodium sulfapyridine, the percentage of acetylated drug in the blood and urine was considerably lower than that found after sulfapyridine itself was given by mouth.

Different subjects varied with respect to their absorption, excretion and conjugation of the different drugs. There were apparently fewer variations with sulfathiazole than with any of the other compounds.

Sulfanilamide was fairly well absorbed from the rectum. All the other drugs were poorly absorbed after rectal administration and this absorption was only slightly better when the sodium salts were used.

The para-acetyl derivatives of sulfanilamide, sulfapyridine and sulfathiazole were poorly absorbed after oral administration. The acetylsulfanilamide was absorbed somewhat better than the others. Only a small percentage of these drugs was deacetylated in the human body.

The four compounds were found to distribute themselves differently between the blood plasma and the red blood cells. Sulfanilamide was found in the red blood cells in greater concentrations than in the plasma, sulfapyridine was about equally distributed, sulfathiazole was present in somewhat greater concentrations in the plasma and sulfamethylthiazole was found mostly in the plasma.

Sulfathiazole was cleared from the blood at a rate which was greater, and sulfamethylthiazole at a rate which was lower than either sulfanilamide or sulfapyridine. The clearance rates of these drugs indicated varying degrees of tubular reabsorption which was greatest for sulfamethylthiazole and least for sulfathiazole.

Data are also presented concerning the concentration of sulfanilamide, sulfapyridine and sulfathiazole in body fluids and organs of 19 patients who died during treatment with these drugs. There were considerable variations among the different cases.

The concentrations of the drugs were higher in the bile and lower in the spinal fluids than in the blood. Sulfathiazole was present regularly in the spinal fluid in about one-third the concentration found in the blood.

Sulfapyridine and sulfathiazole were found in the kidney in considerably higher concentrations than in the blood and other organs. The concentrations of sulfanilamide were about the same in the various organs studied, including the kidney.

In the liver, the amounts of acetylated drug were always less, although the concentrations of free drug were frequently higher than in the blood. This was true of all three drugs.

BIBLIOGRAPHY

1. TAYLOR, F. H. L., LOWELL, F. C., ADAMS, M. A., SPRING, W. C., JR., and FINLAND, M.: A comparative study of the blood concentrations and urinary excretion of sulfapyridine and sulfanilamide after single doses of sulfapyridine and related compounds administered by various routes, *Jr. Clin. Invest.*, 1940, xix, 201.
2. BRATTON, A. C., and MARSHALL, E. K., JR.: A new coupling component for sulfanilamide determination, *Jr. Biol. Chem.*, 1939, cxxviii, 537.
3. STEWART, J. D., ROURKE, G. M., and ALLEN, J. G.: Excretion of sulfanilamide, *Jr. Am. Med. Assoc.*, 1938, cx, 1885.
4. (a) LONG, P. H., and FEINSTONE, W. H.: Observations upon the absorption and excretion of sulfapyridine (2 sulfanilyl aminopyridine), *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 486.
(b) STOKINGER, H. E.: Absorption, acetylation and excretion of 2 sulfanilamid pyridine (Dagenan, M. & B. 693), *Ibid.*, 1939, xl, 61.
5. BROWN, W. H., THORNTON, W. B., and WILSON, J. S.: Observations on the absorption, distribution and excretion of sulfapyridine, Dagenan or M. & B. 693. *Jr. Clin. Invest.*, 1939, xviii, 803.

6. (a) GROSS, P., COOPER, F. B., and LEWIS, M.: Urinary concretions caused by sulfapyridine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 448.
- (b) ANTOPOL, W., and ROBINSON, H.: Urolithiasis and renal pathology after oral administration of 2 (sulfanilylamino) pyridine (sulfapyridine), *Ibid.*, 1939, xl, 428.
7. SOUTHWORTH, H., and COOKE, C.: Hematuria, abdominal pain and nitrogen retention associated with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 1820.
8. STRYKER, W. A.: The nature of the renal lesion with sulfapyridine therapy, *Jr. Am. Med. Assoc.*, 1940, cxiv, 953.
9. VAN DYKE, H. B., GREEP, R. O., RAKE, G., and MCKEE, C. M.: Observations on the toxicology of sulfathiazole and sulfapyridine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 410.
10. LONG, P. H., HAVILAND, J. W., and EDWARDS, L. B.: Acute toxicity, absorption and excretion of sulfathiazole and certain of its derivatives, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 328.
11. REINHOLD, J. G., FLIPPIN, H. F., and SCHWARTZ, L.: Observations on the pharmacology and toxicology of sulfathiazole in man, *Am. Jr. Med. Sci.*, 1940, cxcix, 393.
12. LONG, P. H., HAVILAND, J. W., EDWARDS, L. B., and BLISS, E. A.: A clinical evaluation of the use of sulfanilamide, neoprontosil, sulfapyridine and sulfathiazole in the treatment of infections, *Mississippi Doctor*, 1940, xvii, 541.
13. WHITTEMORE, W. L., ROYSTER, C. L., and RIEDEL, P. A.: Intravenous and rectal administration of sulfapyridine, *Jr. Am. Med. Assoc.*, 1940, cxiv, 940.
14. BARNETT, H. L.: Lobar pneumonia: Specific treatment by chemotherapy, *Jr. Pediat.*, 1940, xvi, 262.
15. STEAD, E. A., JR., and KUNKEL, P.: Absorption of sulphanilamide as an index of the blood flow in the intestine of man, *Am. Jr. Med. Sci.*, 1940, cxcix, 680.
16. ELDAHL, A.: Pneumonia in adults and children treated with 2 (p-acetylaminobenzene-sulphonamido) pyridine, *Acta med. Scand.*, 1939, cii, 340.
17. SISE, H. S.: The distribution of sulfanilamide and acetylsulfanilamide between cells and extracellular fluid, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 451.
18. HANSEN, L.: Distribution of free and conjugated sulfanilamide and sulfapyridine between corpuscles and plasma in both human and rabbit blood, *Jr. Lab. and Clin. Med.*, 1940, xxv, 669.
19. MARSHALL, E. K., JR., EMERSON, K., JR., and CUTTING, W. C.: The distribution of sulfanilamide in the organism, *Jr. Pharmacol. and Exper. Therap.*, 1937, lxi, 196.
20. CHINN, H., and BELLOW, J.: The distribution of sulfanilyl-2-aminopyridine in the body, *Jr. Lab. and Clin. Med.*, 1940, xxv, 735.
21. MARSHALL, E. K., JR., and LITCHFIELD, J. T., JR.: Some aspects of the pharmacology of sulfapyridine, *Jr. Pharmacol. and Exper. Therap.*, 1939, lxxvii, 454.
22. BETTMAN, R., and SPIER, E.: Concentration of sulfanilamide in human bile, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 463.
23. STEWART, J. D., ROURKE, G. M., and ALLEN, J. G.: Acetylation of sulfanilamide, *Surgery*, 1939, v, 232.
24. CAREY, B. W.: Use of sulfanilamide and related compounds in diseases of infancy and childhood, *Jr. Am. Med. Assoc.*, 1940, cxv, 929.

THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1939

(Seventh Rheumatism Review) *

Part I

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GENERAL INCIDENCE OF RHEUMATIC DISEASES: SOCIAL AND ECONOMIC IMPORTANCE

THAT the rheumatic diseases are a great universal menace was again shown by Tegner; his excellent survey of the problem as it affects the United States, England and Europe should be valuable to all students of "rheumatism." In Great Britain respiratory diseases were the first, nervous diseases next and rheumatic complaints were the third commonest cause for disability benefits.⁴⁸² The incidence of chronic rheumatic diseases in England, Wales and Scotland is "shocking," according to Davidson who with the aid of medical practitioners surveyed 100,000 persons in Scotland. Scottish physicians were required to spend 10 per cent of their time on rheumatic diseases; more than 300,000 persons (6 per cent of the total population of 5,000,000) in Scotland require care for these diseases yearly and more than 50,000 insured persons are totally incapacitated for an average of 60 days yearly. Among the insured population of Scotland about one of every 50 men and one of every 60 women were disabled by muscular rheumatism for a month.⁴⁸² Chronic arthritis is one of the commonest disabilities requiring monetary benefits to United States World War veterans.⁸⁰¹ In previous Reviews^{5, 6} we have cited the incidence of rheumatic diseases in the United States as determined by the National Health Survey. Further data on the scope and method of that survey were given.⁵⁹⁵

The influence of climate on the incidence of rheumatic diseases was debated.

Tegner noted that local patriotism, rather than scientific data, often settled the question. Rheumatism was as common in the hills of Sweden as on the flat lands of Denmark and Holland; it is said to be more common in the cold, damp, seaside parts of England, yet in Scandinavia rheumatism sanatoria are generally placed by the sea. Physicians in European countries with much coast line favored the sea air for rheumatic patients; those in countries with little coast line regarded sea air as dangerous, but those in mountainous countries favored the altitude! Tegner concluded that in the temperate zone, local climate is an unimportant factor in the incidence of chronic rheumatism.

Of greater importance than the general climate is the "micro climate" of home and working place, according to Hill. Cold, damp, atmospheric electricity and cyclonic disturbances are not important. Eskimos and Lapps have much less rheumatism than dwellers in temperate zones who live indoors in badly ventilated, artificially heated city houses. Despite the cold, none of Scott's or Shackleton's arctic explorers had rheumatism; there is little rheumatism in the tropics where people live outdoors. Because of the heat and humidity of their surroundings women who make cotton goods are prone to suffer from atrophic arthritis.⁵⁹⁶

[The exact rôle which climate plays cannot be determined until studies are made under controllable experimental conditions.—Ed.]

DEFINITION OF "RHEUMATISM"

"What's in a name?" According to some,³⁸⁰ "rheumatism" is a totally unscientific term which is used to include a wide variety of unrelated conditions. According to others "all forms of acute, secondary chronic, and

primary chronic rheumatism belong to one nosological entity, the protean appearance of which is not greater than that of tuberculosis" (Levinthal).

CLASSIFICATION OF DISEASES OF JOINTS AND RELATED STRUCTURES

The classification of the rheumatic diseases used in the Massachusetts General Hospital, Boston, was given again⁵; Bauer⁵¹ carefully defined each term. The classification adopted at the Fifth Russian All-Union Conference on Rheumatism was also given (Artemiev).

RELATIVE FREQUENCY OF THE RHEUMATIC DISEASES

The relative incidence of the various rheumatic diseases in the British Red Cross Society Clinic for Rheumatism⁹⁷ in London is given in table 1.

TABLE I
Cases of British Red Cross Society Clinic

	Per cent		
	Men	Women	Total
Group A. With articular rheumatism			
1. Rheumatoid (atrophic) type			
a. Infective	9.7	11.1	10.6
b. Noninfective	2.4	5.7	4.5
2. Osteo-arthritic (hypertrophic) type			
a. Senile	13.0	14.7	14.1
b. Climacteric or other metabolic	3.6	10.7	8.1
3. Gout	8.2	2.1	4.4
4. Trauma	1.2	1.8	1.6
5. Miscellaneous (neuropathic, hemophilic and so forth)	4.0	2.4	3.0
Group B. With nonarticular rheumatism	52.7	46.8	46.7
Group C. Suffering from sequel of rheumatic fever	1.0	1.0	1.0
Group D. Suffering from nonrheumatic conditions	4.2	3.7	3.7

[The column of totals in table 1 does not add up to exactly 100 per cent. The last group (D) was probably sent in with supposed "rheumatism." To get the relative incidence of the "rheumatic cases" Group D should really be subtracted from the total group and the figures recalculated.—Ed.]

DISEASES OF JOINTS RELATED PRIMARILY TO TRAUMA

Traumatic Arthritis and Synovitis. Among 193 cases of athletic injuries to knees were 19 of synovitis, 59 of sprains to lateral ligaments, and 115 cases of injuries to semilunar cartilages.³⁹⁴ Acute traumatic arthritis

and synovitis should generally be treated conservatively by rest, heat, light massage and early motion. Rest can be enforced by using bilateral rubber sponge splints surrounded by an elastic bandage⁷⁷⁷ or by plaster casts with a removable top to permit massage and motion.³¹⁸ According to Funsten early aspiration of blood from an injured joint may be dangerous; it may prolong hemorrhage; the knee may not have reacted yet to the trauma and developed resistance to infection: such joints should not be aspirated until 48 hours after trauma, nor be operated on until four to seven days after trauma. Occupational therapy may hasten recovery.⁴¹⁶

Excision of the patella was done by Berkheiser in two cases of traumatic arthritis in knees. The treatment of injuries of the acromioclavicular and sternoclavicular joints was described.⁴⁰⁷ A method for gauging the amount of articular disability after injuries was reported.⁷³³

Sprains. Sprains should be treated by only a few days of rest, followed by use of the joint.⁹⁰ Local injections of novocaine, strapping of the joint with elastoplast, and then careful use of the part were recommended.²⁸⁰

Internal Derangements of Knees. Several articles thereon appeared.^{96, 249, 297, 501, 509, 690, 731, 777} Diagnostic features of various derangements were reviewed.⁴⁸⁰ Injections of air were considered of value in the diagnosis of internal derangements.³⁶¹ The commonest result of injury to knees is damage to the internal semilunar cartilage.^{394, 650} Such injuries may not produce definite locking; according to Edmunds the most valuable symptom is instability of the knee. The results of Hopkins and Huston from surgical treatment (good in 65 per cent) were better than those from conservative measures (good in 45 per cent), but since conservative measures gave relief so often, surgical treatment was reserved for those not helped otherwise. Conservative measures were favored by others also: for semilunar injuries, reduction by manipulation in abduction, a plaster cast for three to four weeks, then the use of exercise and a Thomas heel,²⁴⁹ or reduction of dislocation, aspiration, and use of bivalved cast⁶⁶⁰; for injuries to cruciate ligaments, immobilization for two to four months in a position of slight flexion.^{249, 501}

Described were operations for the repair of the various ligaments of the knee.^{137, 138, 506, 731, 780, 809} Good results were obtained in 83 per cent of Campbell's cases,¹³⁷ in 94 per cent of Schoenfeld's cases.

An experimental study of injuries to ligaments of knee joints in rabbits and in human cadavers was made by Horwitz³⁹⁸: in rabbits tears in the internal lateral ligaments healed regardless of the size of the defect and whether or not fixation was employed. Tears in cruciate ligaments did not heal during simple fixation, and the severed ends could be approximated surgically only early after injury. Satisfactory results of conservative fixation in humans with tears in cruciate ligaments are really due to healing of associated injuries to the collateral ligament.

Bone Rarefaction after Articular Trauma. After trauma to a wrist or ankle, bones of adjacent hand or foot may rarefy, and regressive changes may occur in overlying tissues (muscular atrophy, vasomotor and trophic

changes in skin, perhaps swelling of soft parts). The pathology of Sudeck's atrophy or Leriche's disease is unknown. According to Jaffe long bones may likewise rarefy after trauma (without fracture) to large joints. Biopsies in two such cases indicated that rarefaction was due to hypervascularization of affected tissues especially of cortical bone, and pain arose from functional strain on weakened bones. Recovery is favored by physical therapy and use of affected parts.

Penetrating Wounds. Perforating and penetrating wounds of joints, such as result from air-attacks in war, demand early excision of the wound.^{288, 319, 540, 541, 601, 743} Recommended were articular lavage with normal saline or a mild antiseptic solution, removal of foreign bodies, suturing the synovial membrane, and packing the cutaneous wound with vaseline gauze. Immobilization of the part in plaster was not recommended for at least four days after excision lest gas gangrene and tetanus infection be undetected.⁵⁴¹

[Would not prophylactic tetanus antitoxin and chemotherapy be adequate protection against such infections?—Ed.]

GONORRHEAL ARTHRITIS AND GONORRHEAL "RHEUMATISM"

Incidence. In the United States navy gonorrhea still holds first place as a cause of sick days in hospital, equaling 100,000 per year.⁵⁸⁹ Within six years the annual rate has fallen from 85 to 44 cases per 1000 men. Arthritis occurred in about 2 per cent of these cases.⁵⁸⁹ The greatest factor in producing this improvement has been the realization of the feeble worth of chemical prophylaxis ("little more than a superfluous ritual, something like the use of a finger bowl at the conclusion of a dinner") and substitution of rubber prophylaxis which is almost 100 per cent effective.

Rosenthal and Weinstein urged more energetic campaigns, using epidemiologic methods, in cases of juvenile gonorrhea.

Clinical Data. There were many reports on gonorrhea and its complications.^{190, 311, 344, 382, 405, 431, 645}

Gonococcal tenosynovitis of flexor tendons of hands is more common than was supposed. The gonococcus was responsible for a third of the cases of tenosynovitis seen by Hamlin and Sarris. Absence of a history of trauma in a case of gonorrhea, in which signs and symptoms of tenosynovitis appear less severe than the duration of the disease would suggest, should lead one to suspect its gonococcal nature. A positive smear or culture of pus obtained by aspiration confirms the diagnosis. If aspiration yields insufficient pus, incision with primary closure is recommended.

Diagnosis. No new data on the diagnosis of gonorrheal arthritis were noted.

Blankenhorn warned against mistaking gonococcal arthritis for rheumatic fever and reported the case of a 14 year old negress to illustrate the point. Marked im-

provement resulted after three days of sulfanilamide; none had occurred from sodium salicylate.

[A migratory polyarthritis is common during the first week of gonorrheal arthritis. Chills, which often occur at the onset of gonorrheal arthritis, rarely occur in rheumatic fever.—Ed.]

Unusual Features and Complications. Five cases of gonococcal endocarditis with two recoveries were reported.^{299, 372} Gonorrheal arthritis and meningitis with recovery were observed in a woman aged 29 years, by Steiner.

[It seems very probable that this was a case of gonococcal meningitis. To date, only 10 such cases, meeting rigid diagnostic requirements, have been reported; arthritis occurred in seven of the 10 cases.—Ed.]

Norbury reported what he considered to be a case of gonorrheal myelitis. Keratoderma blennorrhagicum was differentiated from psoriasis arthropathica by Epstein whose material consisted of 75 cases of keratoderma blennorrhagicum and 33 cases of psoriasis arthropathica, most of which were gleaned from the literature. The chief distinctions were: (1) the obviously different etiology, (2) the presence of silver scaling lesions in psoriasis, and of pustular keratotic lesions in keratoderma blennorrhagicum, (3) the different site of the lesions, usually soles, palms and penis in keratoderma blennorrhagicum, the extensor surfaces and scalp [and nails—Ed.] in psoriasis arthropathica, and (4) pitting of nails which rarely occurs in keratoderma blennorrhagicum.

[As the author admitted, these two diseases should rarely be mistaken for one another. This paper suffered from the lack of large first-hand observations, which are necessary to make a report authoritative. Failure to state what type of cases were included under the term "psoriasis arthropathica," further weakened it.—Ed.]

Pathology. No new data were presented.

Roentgenograms. No new studies were reported.

Laboratory Data. 1. Identification of Gonococci in Smears. Microscopic examination of smears containing only a few gram-negative intracellular diplococci is greatly facilitated if smears are first treated with 20 per cent trichloroacetic acid (in lieu of heat fixation)¹⁶⁹; this increases the transparency of mucus and cells, and thus renders the recognition of single pairs of gram-negative intracellular cocci much easier. Walton⁷⁹⁵ recommended the modification of the Pappenheim-Saathof formula, by substituting absolute methyl alcohol for 95 per cent ethyl alcohol; this makes for better stability of the methyl green and better differentiation.

[The author admitted: "This stain is not selective for the gonococcus but for the Neisseria group of micro-organisms." The employment of Cohn's¹⁶⁹ modification of the Gram stain will result in fewer diagnostic errors than Walton's method.—Ed.]

2. Cultures of Gonococci. The cultural method (McLeod, 1934; Carpenter, 1937) is the most reliable diagnostic procedure in gonococcal infections. Malcolm and Dolman studied 5391 cultures and corresponding smears from patients with possible residual gonococcal infections. The cultural method uncovered five times as many positive and suspicious cases as did the smear technic, and 648 definitely or possibly infected persons were prevented from being discharged as cured. In one case positive or suspicious cultures were obtained on 13 occasions in 10 months, yet the corresponding smears were negative. Cultures were superior to smears in cases of chronic gonorrhea, but not in acute gonorrhea, according to Winer and Leibovitz. [Many studies indicate the necessity of cultural methods for diagnosis and establishment of cure. Failure to employ this method routinely accounts in part for the unchanged incidence of gonococcal infections in the general population.—Ed.] Most workers employ McLeod's technic (1934) with or without slight modifications. Certain charcoal prepara-

tions (blood or sugar charcoal heated to 1000° C. for one hour, graphite) added to nutrient agar were claimed to enhance the growth of gonococci, especially if the culture is incubated under 1.5 to 5.0 per cent carbon dioxide tension.³²⁰ [This observation was first made by Pelouze, 1931. In most cases this medium is inferior to blood agar.—Ed.]. Cohn noted that gonococci rarely hemolyze a 5 per cent horse blood agar plate, whereas meningococci do after 48 hours' incubation at 37° C.

3. *Gonococcal Complement Fixation Tests.* Cohn¹⁷⁰ studied 59 proved cases of gonorrhea for a year or more to evaluate the gonococcal complement fixation test on patients treated with sulfanilamide. This drug does not affect the specificity of the test (in some cases positive and in others negative gonococcal complement fixations developed under treatment). In 11 cases reactions were negative throughout the disease. This lack of immunologic response occurred because of either the superficiality or short duration of the infection, prevention of its spread by sulfanilamide, or weak reactivity between tissues and organisms. In nine cases of persistent clinical signs and presumably a latent focus, the fixation test was strongly positive during the period of observation. In 21 cases in which clinical and bacteriologic cure resulted, there was serologic reversal from strongly positive to negative reactions. Although patients who responded bacteriologically to sulfanilamide did so in three to five days, the serologic reversal occurred an average of four months (17 days to seven months) later. If the fixation test was weakly positive, reversal was more rapid. Cohn concluded that prompt reversal of the fixation test from positive to negative can be used as a criterion of cure, but it should not supersede clinical or bacteriologic evidence of cure. If fixation tests are positive for over five months, additional clinical and bacteriologic investigations are indicated. Negative fixation tests do not necessarily mean absence of gonococcal infection.

4. *Skin Reactions to Gonococcus Bouillon Filtrates.* The Corbus-Ferry bouillon filtrate when injected intradermally produced positive reactions in 96 per cent of 78 proved cases of chronic gonorrhea and no reaction in 18 per cent of 188 "cured" cases.⁸²⁰ [The test is not diagnostic: false positives often occur in controls; only 32 definitely positive reactions were found in 40 of the proved cases.⁸²⁰—Ed.] Rossett isolated a carbohydrate-like substance from a medium in which gonococci were grown.

[Although this substance tended to cause stronger reactions on the skin of persons with gonorrhea than on the skin of normal persons, from the author's data we cannot conclude that the test is clinically useful or highly specific.—Ed.]

THE TREATMENT OF GONORRHEAL ARTHRITIS

The 1939 literature indicated that chemotherapy (with the sulfonamides) provides the best treatment of gonorrhea and its complications. Fever therapy and other measures generally are now used only as adjuncts to chemotherapy or as alternates when it fails.

Many reports are difficult to evaluate because of (1) failure to employ rigid standards in establishing "cures"; some physicians required, as criteria of cure, negative smears and cultures for six months after resumption of a normal life, and the use of various provocative tests; others were content with disappearance of signs and symptoms of the disease; (2) variations in methods of therapy used; (3) inadequate dosage and irregular administration of the drug given; (4) variations in adjunctive measures (restriction of fluids); and (5) use of several types of treatment, the respective merits of which have not been evaluated separately. Enthusiasm for the sulfonamide group varies greatly. Many consider it the most valuable agent ever discovered for the treatment of gonorrhea. An occasional writer⁸⁰⁶ ad-

vocated "back to the old treatment of gonorrhea," but the basis for such a statement was not adequately given.

Before discussing the treatment of gonorrheal arthritis with the sulfonamides we will first discuss the general topic of the sulfonamides.

SULFANILAMIDE AND ITS DERIVATIVES

Literature pertaining to the sulfonamide drugs continues to be voluminous. Useful reviews on sulfanilamide and sulfapyridine appeared.^{72, 105, 148, 441, 495, 496, 517, 620, 625} In their excellent review Bigler and Haralambie discussed the use of these drugs for children. Having described the mode of action, toxic and therapeutic effects of the sulfonamide drugs in detail in recent Reviews, we shall refer only to reports giving additional information. The drugs most commonly employed are sulfanilamide, sulfapyridine, and sulfathiazole, although experiences with sulfanilyl dimethyl sulfanilamide (uliron, uleron) sulfanilyl sulfanilamide (disulon), benzyl-sulfanilamide (septazine, soluseptazine and proseptasine), prontosil and neoprontosil continue to be recorded. Because sulfathiazole is a less toxic drug it probably will be used more often in the future if it proves to be as effective as sulfanilamide and sulfapyridine.

Mode of Action. Many workers^{88, 281, 442, 497, 509, 556, 600, 718} agreed that these drugs exert a bacteriostatic effect on susceptible organisms, but the mode of action is not yet known. Locke and co-workers^{5, 492} suggested that sulfanilamide depended on its anticatalase effect. This hypothesis did not seem tenable to MacLeod.

Other studies on the mode of action of the sulfonamides appeared.^{281, 718, 724} From these reports it is apparent that the bacteriostatic effect of the sulfonamide drugs is probably dependent on interference with the nutrition of microorganisms.

Studies were made suggesting that sulfathiazole is as effective as sulfapyridine in the treatment of experimental meningococcal and pneumococcal infections⁵²⁷ and that sulfapyridine is superior to sulfanilamide in the control of other experimental infections.⁴⁹⁵

Absorption, Diffusion and Excretion. The absorption, distribution and excretion of various sulfonamides were studied by Brown, Thornton and Wilson, Daniel and Farrell.

Toxic Reactions. Some physicians hesitate to use sulfanilamide or its derivatives because of the possible toxic effects. This attitude is hardly justified; extensive use has proved that these drugs if intelligently administered can be employed with much greater impunity than has hitherto been considered possible. Because their toxic effects were discussed in detail in previous Reviews, this year's analysis will only consider the more serious ones and the particular drug which is most likely to produce them.

No new toxic reactions were observed.^{78, 103, 105, 301, 441, 497} Van Dyke, Greep, Rake and McKee concluded from experiments on animals that sulfapyridine is definitely more toxic than sulfathiazole; the principal pathologic change was renal damage. Studies indicated that sulfathiazole is more rapidly metabolized and undergoes much less conjugation than sulfapyridine.

Minor reactions (see previous Reviews), although frequently observed, do not contraindicate continued use of sulfonamide compounds. Of the more serious complications, granulocytopenia and agranulocytosis are most frequently encountered. They may result from either sulfanilamide or sulfapyridine. They have not been

observed from sulfathiazole. Of five patients with agranulocytosis^{199, 562, 689, 741} from sulfapyridine one died⁵⁶²; another¹⁹⁹ had an associated angina. Additional cases attributable to sulfanilamide were reported^{192, 301, 351, 516}; death ensued in one instance.¹⁹² A significant decrease in the leukocyte count may occur from small doses given over a short time, although in most cases granulocytopenia followed the administration of large doses for long periods. This complication may not develop until days after the drug has been discontinued.⁵⁶² If it appears during therapy, the drug should be withdrawn and excess fluids given. Pentnucleotide and liver extract have not been proved effective, for death occurred despite their use.

[Long and his associates⁴⁹⁸ concluded that when agranulocytosis occurs during therapy the prognosis is good if the toxic reaction is recognized at its inception. This can be assured only by making frequent blood counts.—Ed.]

Hematuria with renal and ureteral pain and nitrogen retention occurred during sulfapyridine therapy^{600, 714}; they disappeared promptly when the drug was stopped and extra fluids were given. Oliguria, anuria and azotemia have been observed only from sulfapyridine and sulfathiazole. Anuria is probably due to deposition of acetylsulfapyridine and acetylsulfathiazole crystals in renal tubules, occasionally to blocking of ureters and renal pelves by calculi of these two salts.

Acute hemolytic anemia occurred thrice as often from sulfanilamide as from sulfapyridine. Acute hemolytic anemia from sulfathiazole has not been reported. Koletsky observed hemolytic anemia on the third day of sulfanilamide treatment. The erythrocyte count began to decrease on the second day of therapy and continued to decrease until death on the fifth day. Necropsy revealed erythropoietic hyperplasia of bone marrow, iron pigmentation of liver and spleen, and pallor of viscera. Koletsky pointed out that both his and Woods' (1938) patient had syphilis.

Peripheral neuritis, a rare complication, can result from any of the three commonly employed sulfonamide compounds, although it occurs less frequently from sulfanilamide than from sulfapyridine or sulfathiazole; another case was reported.⁷⁹⁷

[Similar complications have occurred more often with sulfamethylthiazole, sulfanilyl sulfanilamide and sulfanilyl dimethyl sulfanilamide.—Ed.]

Cyanosis. Measurements of functioning and nonfunctioning hemoglobin were made⁷³ on the blood of nine patients given sulfanilamide in an attempt to relate them to the degree of clinical cyanosis. Correlation was not possible; the cause of cyanosis on treatment with sulfanilamide is not established. [Cyanosis observed during sulfanilamide therapy is not due solely to sulfhemoglobinemia or methemoglobinemia.—Ed.] But Wendel generally demonstrated methemoglobin in blood, both spectrophotometrically and by the Van Slyke method, during sulfanilamide therapy. Cyanosis disappeared when 0.1 to 0.2 c.c. of a 1 per cent solution of methylene blue was administered orally each day. [Wendel's idea that methemoglobin is the best explanation of the cyanosis is at variance with the conclusions of Biglow and Werner and others.—Ed.] Cyanosis is less marked with administration of sulfapyridine and minimal with sulfathiazole.

Summary. Those interested in the relative toxicity of the sulfonamides most commonly used should consult a recent article by Long and co-workers.⁴⁹⁸

All toxic reactions except leukopenia and agranulocytosis can be recognized by careful clinical examination. Whenever possible, every necessary laboratory method should be used during treatment. Total and differential leukocyte counts, determinations of hemoglobin and examination of urine should be done regularly. Pallor, icterus and rashes are readily detected. Increase in symptoms or appearance of fever are often important warning signals. The urinary output of patients receiving sulfapyridine and sulfathiazole should be recorded to detect the oliguria which can herald approaching anuria. A fresh specimen of urine should be examined daily for erythrocytes whenever oliguria occurs. If a patient has had a serious toxic reaction, he

is likely to have an earlier and more severe reaction if the drug is administered again. If its second administration is indicated, a test dose of 5 grains should be given. If no reaction ensues in 12 hours, the physician may proceed watchfully with another course of therapy in which the doses are increased gradually. With the appearance of moderately severe toxic effects, administration of the drug should be continued with caution and stopped if reactions become severe; then extra fluids should be given. No new data on the prevention of toxic reactions or on contraindications to the use of the sulfonamide compounds were reported.

TREATMENT OF GONORRHEAL ARTHRITIS WITH SULFANILAMIDE

Only four papers^{133, 168, 443, 827} dealt specifically with the treatment of gonorrheal arthritis with sulfanilamide. Except for Caldwell's report results were similar to those reported last year.⁶ Keefer and Rantz divided 14 cases into three groups: (1) those of infected synovial fluid; (2) those of sterile synovial fluid, and (3) those without effusions. They gave 4 to 5 gm. of the drug daily. Best results were obtained in group 1 (five cases): infected fluids were sterilized in three to seven days; despite this, damage to synovial membrane apparently delayed clinical recovery (these patients averaged the longest hospital stay). The four patients in group 2 recovered without articular disability or deformity. Treatment required an average stay in the hospital of 30 days in group 3 (five patients), as compared to 50 days in a similar hospitalized group in which older methods of treatment were used. The arthritis recurred twice after withdrawal of the drug in one case and once in another, but re-administration of the drug was effective each time. Keefer and Rantz noted (1) that concentrations of the drug were about equal in synovial fluid and blood, (2) that often, but not always, the local focus was clinically and culturally cured, (3) that synovial fluid cell counts diminished and fluid accumulated less rapidly with the use of sulfanilamide than with other remedies, and (4) that sulfanilamide did not hinder formation of immune bodies. This hypothesis that the normal immune mechanism must come into play for permanent cure was not substantiated by the work of others.^{168, 170}

Coggeshall and Bauer,^{52, 168} using larger doses, noted within 48 to 72 hours, striking clinical improvement in nine of 14 proved cases, and in two of four probable cases of gonorrheal arthritis. These results were more prompt and satisfactory than those from any other therapy. They further noted (1) sterilization of infected synovial fluids in 48 to 72 hours, (2) cure of the local focus in 17 of the 18 cases, (3) failure of gonococcal complement fixation tests to become positive on three patients with infected synovial fluids who responded promptly (48 to 72 hours) to sulfanilamide, and (4) the largest percentage of cures when the level of sulfanilamide in the blood was 10 mg. per cent or higher.

Caldwell, using moderate (20 grains every four hours) and small (60 grains daily) doses of the drug in eight cases of gonorrheal arthritis, observed rapid subsidence of joint symptoms in five, gradual subsidence in one,

and slight improvement in two. To hasten resolution he splinted affected joints.

[The latter procedure is regarded as of more value by him than by us. We consider incorrect his statement that "simple sterilization of the synovial fluid by use of sulfanilamide will not eliminate the factors making for destruction of the cartilage." Larger doses of the drug, control of fluid intake and determination of concentrations of sulfanilamide in blood would probably have given him better results.—Ed.]

Prompt relief from sulfanilamide was noted in Yandell's case of gonorrheal arthritis. Spink and Flink cured seven cases therewith. Silver and Elliott noted one patient with gonorrheal arthritis who "responded well" to sulfanilamide (details not given) but of 23 such patients previously given the drug only eight were relieved. Seven of the 10 patients treated by Waugh and Dawber with moderate doses of the drug were relieved.

Five cases of gonorrheal tenosynovitis were treated with sulfanilamide, immobilization and heat³⁶²; the associated arthritis of wrist (two cases) and conjunctivitis (one case) subsided "rapidly." Results were "good"; in only two of the cases did slight flexion contractures occur.

The literature of the past three years indicates that best results have been obtained in the treatment of gonorrhea and gonorrheal arthritis when large doses were given at regular intervals, day and night. The fluid intake should be kept constant (2,000 c.c.) and a blood level of 10 to 15 mg. per cent should be maintained. Under these conditions, obvious improvement should begin within 48 to 96 hours.^{168, 443, 591} If it does not, the case is probably "sulfanilamide-resistant" and will require some other form of therapy (alone or in conjunction with sulfanilamide).

Many physicians have been unwilling to treat gonorrhea with sulfanilamide alone, but also have used locally the time-honored chemical agents. But it is difficult to conclude that such combined therapy is superior to sulfanilamide alone. Still others used sulfanilamide, vaccines and local treatment. Better controlled studies will give us the final answer.

[Current studies are making much of the foregoing work outmoded. Many workers now recommend sulfapyridine or sulfathiazole to the exclusion of sulfanilamide.—Ed.]

TREATMENT OF GONORRHEA AND OF GONORRHEAL ARTHRITIS WITH SULFAPYRIDINE

Gonorrheal Arthritis. Reports concerned specifically with the treatment of gonorrheal arthritis with sulfapyridine did not appear in the literature reviewed. Certain workers^{168, 491} advocated its use in sulfanilamide-resistant cases.

Urogenital Gonorrhea. The literature pertaining to its use in the treatment of gonorrhea has increased greatly. The data thus far presented indicate that sulfapyridine is superior to sulfanilamide in the treatment of gonorrhea and its complications. This may be due in part to the fact that patients treated with sulfapyridine received more nearly full doses than did those receiving sulfanilamide.

TREATMENT OF GONORRHEA WITH OTHER SULFONAMIDE COMPOUNDS

Results with the following drugs were reported in cases of gonorrhea but not of gonorrheal arthritis. Results with sulfanilyl dimethyl sulfanilamide (uliron, uleron) varied greatly. Peripheral neuritis was a serious and not uncommon effect of this drug and also of sulfanilyl sulfanilamide (disulon); hence many workers discontinued their use. So little data on the value of benzyl-sulfanilamide (proseptasine, septazine and soluseptazine) were reported that an evaluation of it cannot yet be made.

FEVER THERAPY FOR GONORRHEAL ARTHRITIS

In view of the value of the sulfonamides fever therapy continues to play a subordinate rôle. Only Beach considered it "more certain" than sulfanilamide; other writers recommend it only in cases resistant to chemotherapy. A few reports concerned the effect of fever therapy alone: "cures" were obtained in from 25 to 70 per cent; little or no relief resulted in 10 to 30 per cent of the cases; in the rest improvement was moderate to marked. Fever sessions were usually for five to eight hours at 106 to 107° F. Failures were due to inadequate heating or to residual damage present prior to hyperpyrexia.

None of Gwynn's 76 patients were cured; 80 per cent were markedly relieved. Notable improvement occurred in 73 per cent of Ferderber's 77 cases. Davison, Lowance and Crowe treated 25 patients; 24 per cent were cured, 52 per cent notably benefited, 24 per cent not relieved. Of the 50 patients treated by Johnson and Whiston 88 per cent were markedly or moderately relieved, 12 per cent were not. Bierman and Levenson gave "short fever sessions" (six to eight hours) to 16 patients, seven of whom were cured; long sessions (10 to 12 hours) to 24, 16 of whom were cured. In 54 per cent of Ledbetter's 15 cases cure was obtained; in 33 per cent notable relief. [The average fever session was only three hours at 106° F., an amount often insufficient.—Ed.] Of Bromberg's 40 patients, 80 per cent were cured. Cures were "expected" in 70 per cent by Cheetham; 90 per cent of Neymann's patients (unstated number) were cured or markedly relieved. Vassiliadis reported cures in four cases and Gottesman in 12 of 14.

Reactions to fever therapy were few: temporary respiratory collapse occurred in two cases and neuronitis in five,²¹⁹ shock in three of 300 cases¹⁵² and death in one case (no details).²⁶⁹ The proper technic of fever therapy was again described.^{71, 253, 269, 274, 479} Ishmael favored the use of fever therapy plus autohemotherapy.

FEVER THERAPY COMBINED WITH SULFANILAMIDE FOR GONORRHEAL ARTHRITIS

Several physicians considered the combined use of fever therapy with chemotherapy better than either alone and recommended this combination in cases of sulfanilamide-resistant gonorrheal arthritis.^{42, 71, 253, 274, 540, 558, 578} The combination was said to be successful in from 90⁴² to almost 100 per cent⁵⁷⁸ of cases resistant to either alone. Some writers⁵⁷⁸ used sulfanilamide for three or four days prior to one 10-hour fever session. Others²⁷⁴ gave

5 gm. of sulfanilamide daily for two days, then six or eight hours of fever (106.4° F.); of 14 patients so treated 11 were cured. According to Muether and Andrews, fever produced by typhoid vaccine ("more economical than that from machines") plus the use of neoprontosil reduced the stay in the hospital in eight cases of gonorrheal arthritis by "about 50 per cent."

[Details in most of these reports were meager; the number of patients treated was small, the control material inadequate for a final appraisal of combined therapy. Further studies thereon are to be desired.—Ed.]

Fever therapy does not alter the concentration of sulfanilamide in blood except as it slows intestinal absorption of the drug. Sulfanilamide with fever therapy does not increase the hazards of the latter.⁴⁸⁴

OTHER REMEDIAL AGENTS FOR GONORRHEA AND ITS COMPLICATIONS

Corbus and Corbus again advocated the use of the Corbus-Ferry bouillon filtrate in the treatment of gonorrhea and its complications. Chrysotherapy did not produce benefit in four cases of gonorrheal arthritis.⁴⁵²

FEVER THERAPY: GENERAL DISCUSSION

Methods. The development of artificial fever and methods for its production were discussed.^{102, 274, 314, 331, 466, 469, 473, 474, 558, 587, 597, 644, 709} Results and hazards were considered about equal, whether fever was produced by the induction method, by hot moist air or by hot sprays of water. Many workers^{42, 71, 473, 578} favored 10 to 12 hour fever sessions, especially in gonococcal infections, either with or without sulfanilamide and with additional local pelvic heating.⁷⁰

Preparation of Patient and Management during Fever. Those who use fever therapy are referred to several reports on the preparation of patients for fever treatments^{455, 473, 474, 479, 597, 658} and on their management during fever.^{107, 294}

Complications, Untoward Results. Careful selection and management of patients during fever sessions has made the procedure relatively safe. Minor reactions (headache, nausea, vomiting, tetany, muscle cramps, herpes labialis) were common.^{474, 479, 559} Serious reactions like neuronitis²¹⁹ and other neurologic changes, some of which were transient, some permanent,¹⁸¹ were rare. Three deaths from fever therapy occurred.^{269, 314, 486} The parenchymatous, necrotic, hemorrhagic and congestive changes that can affect tissues, especially the liver, from overdoses of fever were studied.^{348, 817}

TUBERCULOUS ARTHRITIS: GENERAL COMMENT

Incidence. The incidence of tuberculous arthritis is still decreasing. The recent admission rate for osseous tuberculosis per 1,000 admissions was 1.58 in the Charity Hospital, New Orleans, 2.27 in the El Paso City-County Hospital.⁹⁵ In a New York hospital fusion operations on tuberculous knees have decreased in number to a third of that 10 years ago.⁷⁷²

Clinical Data. New cases of tuberculous arthritis were reported: knees were affected in 222⁷⁷² and in 47 cases,⁵²⁸ spine, hips or knees in 71,⁹⁵ and various joints in 310.¹⁶⁰ Trauma preceded articular symptoms in only 37 per cent of Toumey's cases. The incidence of pulmonary tuberculosis in cases of tuberculous arthritis has varied in different series from about 10 to 70 per cent; it was 20 per cent in that of Breck and Basom. The disease usually affects children; of Le Cocq's patients 85 per cent were children less than 10 years of age. Blood proteins are only slightly altered.⁶⁷¹

Diagnosis. Early specific diagnostic signs may be absent.⁶⁷² Roentgenograms in early stages of the disease are quite nonspecific,⁷⁷² but when roentgenograms reveal swelling of soft tissue, haziness of detail, preservation of joint space and localized bone atrophy, tuberculosis should be considered.⁴²⁶ Mantoux tests are usually positive but may be negative even in proved cases of tuberculous arthritis.⁶⁷² Of greatest value for early diagnosis are biopsy of synovial membrane and aspiration of fluid for guinea-pig tests. Both should be done; one may be positive, the other negative.⁷⁷² In 82 per cent of Toumey's cases (knees), biopsies revealed tubercles; frozen sections are inferior to permanent sections. Since biopsy of a joint is not without danger Seddon recommended biopsy of inguinal glands on the same side as the affected knee. Tuberculous inguinal adenitis does not exist as an isolated disease. In 15 (80 per cent) of 18 proved cases of tuberculous knees, biopsies of inguinal glands revealed tuberculous adenitis either by section or guinea-pig test or both; they were negative for tuberculosis in only three cases. Although a "negative biopsy" of inguinal nodes does not exclude tuberculous arthritis in an adjacent arthritic knee, a "positive test" is strong and reasonably accurate presumptive evidence.

Treatment. The current tendency is to treat children conservatively at least for awhile,⁶⁷⁹ but to treat adults surgically by some fusion operation, except that one may temporize for awhile when an upper extremity is affected.⁹⁵ Cleveland's statistics prove again that the disease is serious and the mortality high. Operation alone will not effect a cure but may turn the tide in favor of the patient. End results depend on the type and extent of the infection. The mortality noted by Cleveland was 48 per cent among patients with pulmonary tuberculosis and positive sputum, or pulmonary tuberculosis, negative sputum and metastatic disease, 10 per cent among those without pulmonary disease, or with pneumonitis, negative sputa and no metastatic disease (aside from joints).

[Fusions should be done, not during the acute progressive stage, but only when the articular lesion has become relatively quiescent through immobilization.—Ed.]

TUBERCULOUS ARTHRITIS: SPECIAL LOCALIZATIONS

Joints affected are, in order of frequency, spine, hips and knees^{95, 478}: of the 330 affected joints in Cleveland's 310 cases 95 per cent were weight-bearing joints.

Spine. Early diagnosis of spinal tuberculosis presents many difficulties.⁸⁹ The details of Cleveland's 173 cases of tuberculous spondylitis were given: any vertebra, but especially the seventh thoracic to the fourth lumbar vertebrae, were affected.

Tuberculous spondylitis may roentgenographically simulate malignancy, nonspecific infections, lymphogranuloma inguinale, congenital or traumatic lesions, but especially well-encapsulated and localized suppurative spondylitis from staphylococci or streptococci of low virulence. One patient²⁸⁷ presented what could only be considered traumatic spondylitis until the premortem appearance of tuberculous meningitis and miliary tuberculosis a year later. In a case of apparent spinal malignancy spontaneous fractures developed from tuberculosis in 14 ribs, as well as the spine.³⁶⁶ In a case of Pott's disease earliest symptoms were those of tuberculous "meningitis sympathica"; tuberculous spondylitis was discovered months later.⁶⁹⁸

"Having seen all cases under conservative treatment go on to deformity, dependency and destruction" Bosworth strongly recommended in all cases a Hibbs' fusion operation reinforced by long iliac grafts, to be done as early as possible. But others^{705, 746} were pessimistic about results of surgical treatment. Such treatment prevents collapse but results are "not satisfactory." Partial fusion generally results, but not "complete bony fusion," hence the disease too often progresses. A good "class A" result was obtained after fusion in only 12 of Smith's⁷⁰⁵ 49 cases. Results of fusion were excellent in 54 per cent of Cleveland's cases.

Hips. When hips are affected, multiple foci, often too small to be seen in roentgenograms, are usually present. Among Cholmeley's 55 children the commonest foci were in the mesial and lateral half of the acetabular roof and in the femoral neck. To detect them serial roentgenograms were taken in different planes. Farkas devised a new operation to provide more complete immobilization. Albee and Shands favored extra-articular fusion by tibial grafts rather than intra-articular fusion.

Knees. London practitioners are now (correctly) suspecting tuberculous arthritis of knees early, long before the classical picture appears, often too early for roentgenograms to support the diagnosis.⁶⁷² Differentiation in early cases must be made from gonorrheal and atrophic arthritis.⁷⁷² After several months to a year of illness roentgenographic diagnosis becomes more certain, but in 32 of Toumey's long standing cases no clinical or laboratory proof of tuberculosis was obtained until operation. Although they approve of "radical" (i.e., surgical) treatment of tuberculous knees in adults, many orthopedists avoid operations on children under 15 years so as not to interfere with bone growth or produce shortening of legs. But McKeever and Toumey considered such conservatism faulty. After an average of three years of conservative treatment given to McKeever's 47 juvenile patients, the disease was still active in every affected knee. His statistical results from "economical resection" to produce femoro-tibial synostosis were su-

perior. Among Toumey's 222 cases in which fusions were done, solid fusion resulted in 196. Results of fusion were "excellent" in 54 per cent of Cleveland's 57 cases.

Other Sites. Tuberculous tendinitis and bursitis are uncommon: three cases affecting hands were reported.⁶⁰³

Osteitis Tuberculosa Multiplex Cystica. This disease, first described by Jungling (1920), generally affects small joints; only Elliott (1935) has previously reported involvement of large joints (two cases in knees). In one case a knee and elbow were proved to be tuberculous at the time of fusion; over 10 years later, when seen by Warner multiple tuberculous cysts had developed in the firmly ankylosed knee and elbow.

"*Tuberculous Rheumatism.*" No reports of this supposed [but very doubtful—Ed.] entity appeared.

PNEUMOCOCCAL ARTHRITIS

With the advent of highly effective chemotherapy against pneumococci, pneumococcal arthritis appears to be diminishing almost to the vanishing point. No cases were reported in the literature for the year. Shaffer and Bennett in an experimental study on rabbits, reported that virulent pneumococci, type III, when injected intravenously, rapidly gained access to joints and within 24 hours nearly all animals had involvement of one or more joints. Cocci were demonstrated in joints when blood and other organs were sterile. They attributed the localization of so-called arthropathic strains of bacteria to the small amount of tissue intervening between the blood vessels and the joint cavities.

[Many reports on the successful chemotherapy of pneumococcal infections with sulfapyridine appeared. But since then a new agent, sulfathiazole, has been extensively used against pneumococcal infections; it appears to be as effective as sulfapyridine and its toxicity is considerably less.—Ed.]

SYPHILITIC ARTHRITIS AND SYNOVITIS; CHARCOT (TABETIC) JOINTS

Syphilitic Arthritis. Syphilitic arthralgias may characterize earlier phases of syphilis; syphilitic arthritis is usually a tertiary lesion (Jostes and Roche). But a mild arthritis "of minor significance" may occur in the secondary stage, and hydrarthrosis may recur during the entire course of syphilis. During the secondary stage "the joint may be invaded secondarily from a neighboring periostitis, osteitis or osteomyelitis." A common late arthritic involvement is chronic synovitis with periarticular thickening and synovial hyperplasia; chronic hydrops may occur. Gummatous osteo-arthritis may involve larger joints, e.g., knees, and cause articular enlargement with tense, shiny skin but no inflammation or impairment of mobility. Ankylosis does not occur unless secondary infection intervenes. Blood proteins were only slightly altered in five cases of syphilitic arthritis.⁶⁷¹

Charcot Joints. The etiology, pathology and symptomatology of these

lesions were discussed.^{309, 521, 685} Sherwood and Hutchins reported 15 cases and summarized data on 586 cases from the literature. From 5 to 10 per cent of tabetics develop Charcot joints; multiple joints are affected in a third of cases. Joints are not always painless; Wassermann reactions may be negative in both blood and spinal fluid even when the condition is unquestionably due to *tabes dorsalis*. The speed of development was stressed by Chitty who reported a case in which the first roentgenograms of the hip were negative but five months later there was complete disappearance of the femoral head.

Current writers advocated arthrodesis. McCauley obtained solid fusion in six of seven cases, Cleveland in five of seven cases, and Giannestras in eight of 10 cases reported by him and in 40 of 46 cases culled from the literature. Several writers urged care in selecting cases for arthrodesis, and recommended operation only when disintegration is not too far advanced. In advanced cases and those in which the neurologic disturbance itself produces crippling, arthrodesis is likely to result in failure; hence they recommended instead external support by means of braces. Although antisiphilitic therapy will not halt the articular process it should always be instituted.

BRUCELLOSIS: UNDULANT (MALTA) FEVER

Incidence. The incidence of brucellosis is increasing. The 2,675 cases noted in 1937 probably represent only a fraction of those which occurred.²⁵⁹ Thirty-eight reports concerned its widespread appearance in the United States, Canada, Iraq,⁵⁵ Jerusalem,⁴⁵⁶ and South Africa. "Ditch fever" in Arizona is said to be brucellosis.¹⁸⁵ Acute brucellosis is two or three times as common among males as among females; latent brucellosis affects the sexes equally. The disease is commoner in small towns and rural districts where raw milk is often used. Humans are more susceptible to porcine and caprine strains than to the bovine.⁶⁸⁸ The former produce more severe disease. Porcine strains may affect horses, poultry, dogs and cows; less commonly sheep, mules, rabbits. The disease is commoner in summer: animals are more infectious when calving, and raw milk is a better culture medium in hot weather. Mosquitoes can, but rarely do, transmit the disease.

Clinical Data. The protean manifestations of the disease were described.^{37, 109, 131, 158, 232, 632, 688, 821} The disease must be looked for: mild acute cases often masquerade as "flu," chronic cases as "neurasthenia." A list of 166 symptoms and signs attributed to brucellosis was given.⁵²³ Calder compared the symptoms in his 550 cases to those in Hardy's (1936) series.

Symptoms Referable to Muscles and Joints. Current reports^{131, 259, 633, 704} indicate that arthralgia is common (normal looking joints may be "excruciatingly painful")²⁵⁹ but arthritis is rare. In one case the disease simulated atrophic arthritis.⁶³³ In another it was "indistinguishable from rheumatic fever" but "yielded dramatically to convalescent antiserum"⁷⁰⁴; in two cases hydrarthrosis of knees was present.⁷⁰⁴ Articular effusions occurred in 15 per cent of Strachan's (1932) 268 cases in South Africa; the spine was often affected. Bishop noted one case of spinal involvement:

endosteal and periosteal reactions with resulting sclerosis of vertebral bodies and spur formation. McGinty and Gambrell stated that in the first reported cases undulant fever was regarded as chronic rheumatism (Curry, 1901).

Pathology. The histology of cutaneous reactions to *Brucella melitensis* antigen was described,³⁰⁵ also details of necropsies in two fatal cases.^{538, 609} In one case the disease resembled Hodgkin's disease.⁵³⁸

Diagnosis. This is difficult and depends largely on laboratory tests, the exact interpretation of which is impossible.⁵³⁰ Tests used are (1) cultures of body fluids, namely blood, urine, stools, bile, spinal or synovial fluid, (2) animal inoculation, (3) agglutination tests, (4) intradermal tests with brucellergin, (5) opsonocytophagic test.

Cultures. When positive, cultures give the most reliable evidence. By their special method cultures were positive in five of seven cases of Smith and Poston, but sometimes cultures take 17 days. Cultures have been positive when other tests were negative, but negative cultures do not exclude the disease.^{259, 260, 456} A new culture method was described.⁴⁵⁶

Agglutination Tests. Their significance and interpretation remain as given in our last Review.^{23, 259, 531, 683, 688, 704, 821} A positive test is suggestive; the test is negative in 20 to 30 per cent of acute cases of brucellosis, usually negative in chronic cases and positive in 10 per cent of "normal" persons.

Skin Tests. Skin tests with killed organisms were considered reliable by some,^{109, 632} unreliable by others^{131, 284, 523} who preferred intracutaneous tests with Foshay's antiserum ("positive" in 92 per cent of 24 acute cases, 91 per cent of 541 chronic cases of "probable brucellosis"). Many of the "reactors" in school children and college students, and in adults and children with vague chronic disabilities may have unsuspected chronic brucellosis.^{23, 530, 633}

Opsonocytophagic Reaction. This was considered reliable by some,¹³¹ of limited value by others.²⁶⁰

Therapeutic Test. If brucellosis is present, sulfanilamide will cause a favorable response and the opsonocytophagic activity for brucellae will rise, according to Blumgart and Gilligan.

[Results from sulfanilamide are not always successful.—Ed.]

Conclusions on Laboratory Tests. One test alone is of little value; data from several tests may be valuable; if agglutination, skin and opsonocytophagic tests all give positive reactions, the evidence is nearly specific.¹³¹ A positive test by even one method occurs 10 times as often in cases of brucellosis as among normals; positive reactions to two or more different tests occur 70 times as often among patients with symptoms compatible with brucellosis as among controls. But it is discouraging to find such tests negative "when they should be positive."

Blood Counts. A characteristic blood picture "found in no other disease" was noted by Calder and associates in more than 50 per cent of 300 cases of brucellosis: leukopenia, lymphocytopoiesis and a lymphocytic "shift to the left"; monocytes were not increased, monocyte-lymphocyte ratios were low. Munger and Huddleson noted leukopenia with relative lymphocytosis, monocytosis, basophilia of neutrophilic granules and "liver damage cells."

TREATMENT OF BRUCELOSIS

Since the disease tends to be self-limited it is difficult to evaluate various remedies. Treatment is more successful in acute than in chronic cases.⁵²³

Serums and Vaccines. Three of five patients were cured by a "specific polyvalent serum."²⁸⁴ Brucellin provokes specific immunization according

to Calder; of 180 patients treated therewith 80 per cent became asymptomatic within three months. Smith and Poston preferred immune human serum for acute cases with positive blood cultures and no antibodies, Brucella vaccine for others.

Fever Therapy. Of 15 patients given fever therapy (three sessions of five hours each, 105 to 106° F. rectal) 80 per cent were "greatly improved" although this amount of fever will not kill Brucella organisms in vitro.^{253, 475}

Chemotherapy. In 1939 physicians evaluated sulfanilamide for brucellosis less optimistically than in 1938. Symptoms disappeared under sulfanilamide therapy in all of Condell's five cases, and in two other cases^{46, 490} in which initial doses were about 60 grains daily for three or four days, 40 grains daily for two weeks more. (In only one of these cases were joint symptoms dominant.¹⁸⁵) Results of other physicians were disappointing. Sulfanilamide in "maximum therapeutic doses" produced temporary improvement followed by recurrences in the five cases of Bynum, and in Schroeder's case. The drug influenced the bacteremia but not the clinical picture in six other cases,⁴⁵⁶ and a case of brucellosis with endocarditis was resistant to three courses of the drug.⁷⁰⁶

[In some cases doses were small and not controlled by blood studies.—Ed.]

Results of this therapy seemed "most encouraging" to Blumgart and Gilligan who summarized 30 reports in the literature to date: of 74 cases recoveries were attributed to the drug in 68 (92 per cent), there were failures in six (8 per cent) but relapses occurred after recovery in 14 (20 per cent). Failures and relapses were mostly from under-treatment. "Recoveries" were rapid; symptoms left within two to 12 days. Recommended dosage was about half a grain per pound of body weight per 24 hours, divided in six doses and continued for three to four days after subsidence of fever (example: for a 150 pound man, 4 to 6 gm. or 60 to 90 grains daily); maximal dosage 6 gm. in 24 hours. Response in acute cases seemed better than in chronic cases.⁸²¹

In guinea-pigs the melitensis variety is less responsive to sulfanilamide than are the suis and abortus varieties¹⁵³; this may explain the poor results in the melitensis cases of Kleeberg, Gurevitch and Alkan. Sulfapyridine in large amounts had little effect on Brucella infections in guinea-pigs.³⁵⁷

The "simple, easy and successful" treatment in Ragsdale's 10 cases was intramuscular injections of sodium cacodylate, 0.45 gm. twice weekly. Kaolin was used by Thames to relieve nervous symptoms. Diets high in vitamins with vitamin supplements (B, C, nicotinic acid) were recommended.^{131, 632, 821}

Prophylaxis. Elimination of reactors from herds is costly, impracticable and relatively ineffective.^{232, 688, 815} Pasteurization of milk is more effective. Perhaps the population can be immunized by generalized inoculation against brucellosis and typhoid fever with a mixed heat killed vaccine effective in animals (Kolmer and Bondi). Infected humans may act as carriers; infected urines and stools should be cared for as in typhoid fever.

TYPHOIDAL ARTHRITIS

No reports appeared.

MENINGOCOCCIC ARTHRITIS

No reports appeared.

SUPPURATIVE (PURULENT, SEPTIC) ARTHRITIS

General Comment. Clinical features of suppurative arthritis were reviewed.^{426, 524, 743, 744} Staphylococci cause it in about 50 per cent of cases, hemolytic streptococci in about 25 per cent, miscellaneous bacteria (pneumococci, etc.) in the rest.⁵²⁴ Sweetapple wrote "Synovial fluid is strongly antibacterial while fresh, but excellent pabulum for bacteria when stale. [What is stale synovial fluid?—Ed.] Surgeons have learned to trust in the antiseptic properties of the peritoneum; we are probably too chary of trusting the synovial membranes." In some cases the arthritis is mild and not frankly suppurative, in others suppurative and rapidly destructive. Among McGovern's 24 cases two arose from ear infections; one from nonhemolytic streptococci, the other from a mixed infection of pneumococci and *Staphylococcus albus*. In five cases reported hips were involved.⁹¹

Of Streptococcal Origin. A patient with severe hemolytic streptococcal sepsis (tonsillitis, pneumonia, nephritis, arthritis) was given sulfanilamide by Spink: function of the knee was restored completely. In synovial exudate before treatment cocci were mostly extracellular, after treatment mostly intracellular.

Of Staphylococcal Origin. A case of suppurative arthritis of knee and elbow caused by hemolytic staphylococci was used by Preston to show that the clinical course of staphylococcic arthritis differs in some respects from that produced by other pyogenic bacteria. [The differences were not made clear.—Ed.] In animals infected with "ordinary abscess producing *Staphylococcus aureus*" invasive local lesions with multiple metastatic abscesses developed; in those infected with "toxicogenic *Staphylococcus aureus*" mild, noninvasive local lesions with marked "toxic degeneration of viscera" developed.

For all such cases Preston recommended (1) aspiration of joints; (2) destruction of organisms locally by lavage with specific bacteriophages, (3) prophylaxis against multiple metastatic abscesses by the intravenous use of autogenous bacteriophage, (4) immobilization of joints, (5) destruction of the bacterial toxin by giving transfusions and ascorbic acid which inhibits the hemolytic power of staphylococcal toxin, (6) increasing the patient's general resistance by diets and fluids, (7) restoration of articular motion by physical means.

[The use of sulfapyridine and sulfathiazole may make such remedies obsolete.—Ed.]

Treatment by Surgical Measures. General principles were outlined^{91, 115, 355, 743, 744} as in previous Reviews. Pyogenic infections of feet should be treated like those of hands; this necessitates a knowledge of the interrelationships of joints, tendon sheaths, bursae, etc.¹¹⁵ Patients whose arthritis is not amenable to newer chemotherapeutic agents may require (1) bilateral incisions into joints (often unsuccessful), (2) lavage of joint cavity, (3) closure of joint and immobilization in plaster, or (4) drainage, traction and temporary immobilization.⁷⁴⁴

Reconstructive and stabilizing surgical methods used in 46 cases of residual damage from suppurative arthritis of hips were discussed by Hallock. Reconstruction operations controlled dislocation and pain but limited the motion considerably and the control of pain was not always permanent. Results of arthroplasty were better but the operation was not often possible. "Shelf stabilization operations," gave stable joints but also shortening and a limp. Fusion produced stable painless hips without a marked limp and was the operation of choice.

[Commenting on this paper Key stated: "Every reconstruction operation is a subterfuge. I have never seen one that I liked." Dickson added: "My experience with reconstruction operations and shelf operations parallels that reported. Fusion is by far the most dependable operation." In the future the situation may be improved by the use of two new procedures, chemotherapy, and the Smith-Petersen cup.—Ed.]

ARTHRITIS OF SCARLET FEVER: POSTSCARLATINAL RHEUMATISM

No publications appeared.

RARER FORMS OF SPECIFIC ARTHRITIS

The Arthritis of Bacillary Dysentery. A case of arthritis associated with *Bacillus dysenteriae Flexner* was reported.⁴⁰ Baker referred to 25 cases seen by Dudgeon in Macedonia. In only one of 10 cases studied bacteriologically were organisms recovered from joints; in this case the blood culture was also positive. Baker's patient was a carrier of *Bacillus dysenteriae Flexner*, and, except for a mild episode of watery diarrhea a year previously, was in excellent health. Only one similar case is reported in the literature.

The patient, a man 42 years old, first complained of severe pain in the left wrist, drenching sweats and loss of weight. Temperature varied from 101° to 103° F. Later the right wrist and hand became almost helpless because of pain, swelling and muscle spasm. Hands, wrists, elbows, knees, right shoulder and left hip became involved. Blood and joint cultures were repeatedly negative; the stool contained numerous colonies of *Bacillus dysenteriae Flexner* and the agglutination reaction in the serum reached a titer of 1:640. Roentgenograms were negative. The condition eventually cleared up. Although the etiologic factor was not definitely established, Baker felt the most probable explanation was an allergic response in joints. In such obscure cases he advocated agglutination tests.

Bilateral ankylosis of hips following dysentery (type unstated) was treated successfully by capsulectomy.⁷⁹⁴

Arthritis Associated with Lymphogranuloma Venereum. Arthritis may occur with lymphogranuloma venereum, as noted by Frei (1938) and by Hellerstrom (1929). Two reports on this subject appeared.^{220, 824}

Dawson and Boots reported 24 cases: 1. The arthritis pursues a variable course but usually appears in a chronic, indolent, serous form with a marked tendency to relapse. Intermittent hydrarthrosis is not uncommon. Occasionally joints are acutely swollen, painful and tender. 2. The arthritis is usually polyarticular and has a predilection for knees, ankles and wrists; frequently both knees or both ankles are involved simultaneously. 3. The arthritis persists for weeks or months, but in the cases observed, there was no obvious destruction of bone or cartilage. Except for periarticular swelling and effusion within the joint, roentgenograms revealed no changes. 4. The character of the synovial fluid varied considerably but it was never purulent. 5. Cultures of synovial fluid on common bacteriologic media were sterile. 6. In all cases the Frei reaction was positive and in most cases other evidence of infection with lymphogranuloma venereum was present. Dawson and Boots attempted to demonstrate both the virus and Frei antigen in aspirated synovial fluid; results were inconclusive.

Wright and Logan described osseous changes with lymphogranuloma venereum. Their diagnostic criteria were as follows: (1) clinical symptoms should be those of lymphogranuloma venereum; (2) Frei reaction should be positive; (3) pathologic, bacteriologic, serologic and roentgen studies must rule out tuberculosis, syphilis, gonorrhea, malignant tumors, and pyogenic infections; (4) changes in bones and joints should be evident roentgenologically. Of their three cases two fulfilled all these requirements. In one case destruction of the intercartilaginous lamina and pubic rami was evident. "In the early phases of the disease arthritic and polyarthritic manifestations may occur, although they are not especially common. Chronic arthritis may occur late in the disease. . . . We report two apparently proved cases of bone necrosis associated with lymphogranuloma venereum and a third case in which such an association is highly probable." Sulfanilamide gave successful results in 15 cases of Nair and Chetty.

Haverhill Fever (Rat Bite Fever). A complete account of Haverhill fever (erythema arthriticum epidemicum) was given by Farrell, Lordi and Vogel. Thirteen reported cases were reviewed and one was added. No attempt was made to resolve the conflict as to the etiologic agent which has variously been described as a *Streptothrix*, *Haverhillia multiformis* and *Streptobacillus moniliformis*.

[There are presumably two types of rat-bite fever, (1) Sodoku or Japanese rat-bite fever due to a spirochete, the *Spirillum minus*, and (2) that due to the *Streptobacillus moniliformis*.^{150, 246} Evidence is accumulating that Haverhill fever is the same as the second type of rat-bite fever. Clinically the two resemble each other closely and the etiologic agent appears to be the same in both. The streptobacillary etiology of rat-bite fever was supported by Dawson and Hobby, who showed that demonstration of the spirillum was only possible by injecting the patient's blood into a susceptible animal. It must be remembered that the spirillum commonly occurs as a harmless saprophyte in experimental animals. Dawson and Hobby concluded that the spirillum theory rested on inadequate evidence.

The relationship between *Streptobacillus moniliformis* and "L forms" or pleuropneumonia-like organisms was discussed at the Third International Congress for

Microbiology in New York (1939). Klieneberger held the view that the "L forms" represented a form of symbiosis but Dienes, Dawson and Hobby were of the opinion that the "L forms" represented a variant phase of the *Streptobacillus moniliformis*. This discussion may assume significance in view of the production of experimental polyarthritis in rats by Collier and Findlay and their associates (discussed under Etiology of rheumatic fever).—Ed.]

RHEUMATIC FEVER

Short general articles on rheumatic fever appeared,^{35, 213, 485, 520, 642, 654, 748, 749, 788} also reviews of recent research in the United States³⁷⁶ and Italy.⁶¹⁴ Keil wrote a historical note on Edward Jenner's lost manuscript on "Rheumatism of the Heart"; the mystery surrounding that important paper remains unsolved.

Incidence. Among 1000 persons under 17 years of age Leslie found 90 who had either a history or physical findings suggestive of "possible rheumatic fever or rheumatic heart disease." But more detailed study of these 90 revealed that only eight had definite, and nine "suspected" rheumatic carditis. Eleven others gave a past history of rheumatic fever (chorea in five instances) but had no residual cardiac damage. Juvenile rheumatic carditis is the commonest single cause of persistently irregular school attendance in London.³⁵ It accounted for 26.7 per cent of all children out of school three months or longer in 1936. The Public Health Department of London listed as rheumatic 22,800 children under 15 years of age or 2.6 per cent of the total child population of 878,000. But apparently the disease in London is now less severe, since the incidence of rheumatic carditis reported by school physicians decreased from 2.0 per cent in 1926 to 0.77 per cent in 1937, and Glover reported a fall in the crude annual death rate from rheumatic fever and its sequelae in England from 67 per 1,000,000 persons in 1901 to 22 in 1937. The incidence of rheumatic fever is decreasing in the United States also.⁷⁴⁸

In the United States there are probably 1,000,000 persons with rheumatic carditis, according to Hedley; the disease causes 40,000 deaths annually.³⁷³ The incidence of rheumatic carditis among public school and college students is 0.5 to 1.0 per cent; data on the incidence of rheumatic fever among sick children were given for three states (Hedley). Pounders and Gray found 122 cases of rheumatism among 3601 pediatric admissions to hospitals in Oklahoma, an incidence of 3.4 per cent. In Oregon, Bilderback and Overstreet noted rheumatic fever and chorea in 3.45 per cent of 4197 medical hospital admissions. Thompson⁷⁶⁴ found a clinical incidence of rheumatic fever of 3.0 per cent among the pediatric patients and rheumatic lesions in 4.27 per cent of the patients coming to necropsy at the University Hospital, Omaha, Nebraska. (Comparable figures indicate an incidence of 4.67 per cent at the Peter Bent Brigham Hospital, Boston and of 0.23 per cent at the Charity Hospital, New Orleans.)

The incidence in Ceylon was given (Fernando): clinical evidences of rheumatic fever were noted in 2.2 per cent of hospital admissions; pathologic evidence was found in 41 (3.6 per cent) of 1110 necropsies.

Predisposing Factors Governing Incidence. 1. Geography and climate. Rheumatic fever is "a very frequent disease in Northern Italy, especially in regions with a continental climate,"⁶¹⁴ and in Vancouver "a comparatively mild disease."³⁹ The disease in Ceylon resembles that in temperate climates.²⁷¹ The disease is the same in arctic Russia as in Leningrad.³²⁹

Studies on dampness and various meteorologic influences threw little

light on the problem. Some^{35, 74} found no correlation between cold and damp and rheumatic fever; others⁶⁰⁵ considered dampness a factor.

2. Season. The marked seasonal incidence of rheumatic fever was again noted. But differences between seasonal curves for the United States and those for England were not as reported in the past. Thus in Oregon and Oklahoma^{74, 605} incidence was highest from December to March and lowest from June to September, while in London it was highest from October to February and lowest from July to September.^{35, 321}

3. Social and hygienic factors. The importance of poor housing, inadequate or improper food, and crowding was stressed by Swift and Cohn who noted frequent relapses among children shortly after their return from convalescent homes to their usual home environment. Among one London group of rheumatic children³⁵ 20 per cent came from "very poor" homes while only 1.4 per cent were from "very good" homes. But the authors noted the danger of drawing conclusions from such an analysis because the population studied was made up chiefly of poor families and did not represent a true cross section. In this study overcrowding was not found to add any "greater risk." According to Glover the disease is 20 to 30 times more frequent among poor children than among rich. The diet of most rheumatic children in London appeared to Jones and Taylor to be adequate.

4. Family, heredity, and constitution. Families of 96 rheumatic children in Baltimore and of 33 nonrheumatic children (controls) were studied by Gauld, Ciocco and Read. A family history of rheumatic fever was obtained 3.7 times as often in the case of rheumatic children as in the controls. "When one or both parents had a history of rheumatic manifestations a greater percentage of the offspring was rheumatic than was found in the offspring of parents who gave no history of rheumatic disease." The percentage of rheumatic female offspring of rheumatic mothers was twice as high as that of rheumatic male offspring, and rheumatic fever was more prevalent among maternal than paternal aunts and uncles. Hence hereditary constitution may play a rôle in the predisposition to rheumatic fever. Sundell described two constitutional types of children predisposed to rheumatic fever. [No data supported this contention which is doubted by many.—Ed.] Hedley noted that the disease is less frequent but more fatal among negroes than white people.

5. Sex. Among 8,000 rheumatic children in London³⁵ the ratio of boys to girls was 3:4.2 but girls tended to have milder disease. Thus, among 4774 admissions to special juvenile rheumatism units, 40.2 per cent of the boys and 37.4 per cent of the girls gave evidence of cardiac involvement while among 1152 children at the time of dismissal from such units the figures were 38 per cent and 33.3 per cent respectively. In a group of 122 children⁶⁰⁵ the ratio of boys to girls was 4.3:5.7, while in another group of 116, boys predominated (57 per cent) except for chorea which occurred 19 times among the girls and 14 times among the boys.

6. Age. The highest incidence of initial attacks occurred at the age

periods of 6, and 11 to 13 years.^{74, 605} Bach and his co-authors considered the dangerous period, that from 5 to 12 years; rheumatic fever is "exceedingly rare" in children under 3 years of age; after the age of 11 years it diminishes "until at 14 the risk is one-half that at 5."

SYMPTOMS AND CLINICAL MANIFESTATIONS OF RHEUMATIC FEVER

General Comment. Among 1068 rheumatic children studied by Gibson³¹² 459 had had chorea, 650 polyarthritis and 627 cardiac involvement. Of those with chorea, 208 had had no other rheumatic manifestation, 104 had had polyarthritis also, 176 (38 per cent), cardiac involvement and 24, nodules. Among the 650 children with polyarthritis, 157 had only had arthritis, 164 had chorea, 420 had cardiac involvement and 87 had nodules. Of the 627 with heart disease, all but 97 had had either joint pain or chorea. In another series of 122 patients⁶⁰⁵ the incidence of symptoms was as follows: carditis, 83 per cent; arthritis and carditis, 59 per cent; chorea, arthritis and carditis, 20 per cent; carditis only, 10 per cent; arthritis only, 9 per cent; chorea and carditis, 9 per cent; chorea only, 6 per cent, and subcutaneous nodules, 4 per cent. [A low incidence of nodules.—Ed.] In London "all clinicians agree that the type of case characterized by acutely swollen joints, sour sweats and severe prostration is now rarely seen."

[One could not make so broad a statement as that in New York City.—Ed.]

Cardiovascular Symptoms. The importance of distinguishing between carditis and inactive rheumatic heart disease was stressed.^{78, 436, 748, 754} A classification of the degree of activity of infection based on the percentage abnormality of leukocyte counts was devised.⁴³⁶ Taussig stated that in children with inactive rheumatic valvular disease further cardiac enlargement does not occur once the heart is adjusted to new conditions imposed by valvular inefficiency; but it does occur when active carditis recurs. The importance of myocardial damage as a cause of cardiac failure in rheumatic carditis has been overemphasized; valvular damage is the important factor (Massie and Levine).

[These authors apparently fail to realize that the most important factor in rheumatic heart disease is that of infection. Doubtless the chief cause of cardiac failure in active carditis is myocardial weakness. What the relative importance of myocardial and valvular damage is in inactive rheumatic heart disease is not so clear.—Ed.]

Parker and Willius noted the difficulty of determining whether massive cardiac enlargement in some cases is due to pericardial effusion or to myocardial dilatation. An analysis of patients with mitral stenosis was made.²²⁹

Electrocardiographic studies were made in cases of inactive rheumatic heart disease.^{18, 220, 518, 629} In 48 per cent of 100 cases studied by Ritchie the auriculoventricular conduction time was greater than 0.19 second, or bundle-branch block or partial auriculoventricular block was present. [In the remaining 52 per cent electrocardiograms were normal in 20, undescribed in 32.—Ed.] Chest leads were used in 10 cases and in two revealed T-wave abnormalities not seen in standard leads. "Rheumatic cardiac patients with persistently prolonged P-R interval are much more likely to develop auricular fibrillation than those whose P-R interval is normal."¹⁸

Various roentgenologic aspects of rheumatic carditis were presented.^{477, 586, 713, 754} Several authors considered anoxemia a cause of myocardial weakness in rheumatic

carditis.^{604, 629, 748} Poulton, questioning whether toxins play any part in this, stated that the electrocardiographic changes of carditis can be caused by lack of oxygen and reported differences in the lactic acid content of blood and urine of rheumatic subjects and controls which, he thought, indicated anoxemia.

[No figures were given; the evidence was not convincing. But doubtless anoxemia does contribute to the myocardial weakness in carditis.—Ed.]

The arm to tongue circulation rate in pregnant women with well-compensated rheumatic heart disease is normal but is prolonged when cardiac insufficiency occurs.¹⁵⁷

Arthritis. Formerly it was taught that growing pains indicate rheumatic fever, but this is not often the case. The differentiation between those of rheumatic and nonrheumatic origin was given.^{372, 681, 754, 812} Nonrheumatic pains of children tend to come at the day's end, are in muscles of legs and thighs rather than in joints, seldom involve upper extremities, and are not associated with other signs of rheumatic activity or with abnormal sedimentation rate, leukocyte count or hemoglobin. [They usually represent muscle fatigue from overactivity.—Ed.] The subsequent incidence of carditis in children with nonrheumatic "growing pains" is no greater than that in the general juvenile population.³⁷²

Subcutaneous Nodules. The incidence of subcutaneous nodules in rheumatic children was 1.0 per cent and 4.0 per cent respectively in two American reports.^{241, 605} Fernando found no nodules among 214 rheumatic patients in Ceylon (only nine of his patients were under 10 years of age).

Chorea and Other Neuropsychiatric Manifestations. Schlesinger reviewed briefly the subject of chorea. Of Bauer's⁵¹ 70 choreic patients, 51 had cardiac damage from previous rheumatic episodes or sustained during the chorea. Every one of the 70 had "undoubted rapid sedimentation rates upon admission" and Bauer stated that "careful study will reclassify supposed choreics with normal sedimentation rates in other disease groups." This is contrary to the experience of others,^{31, 35, 252} that sedimentation rates are normal in choreics without other rheumatic symptoms.

Ten of Ritchie's 179 rheumatic patients had delirium. One developed cerebral edema with terminal epileptiform attacks. Another had severe headache and rigidity of neck but necropsy revealed no evidence of meningitis. [See section on "pathology of rheumatic fever."—Ed.] Organic lesions of the brain caused by rheumatic fever can induce such varied psychiatric syndromes as dementia praecox, manic-depressive or involutional and senile psychoses, psychosis with cerebral arteriosclerosis and mental deficiency.^{111, 112}

[Probably most investigators in the fields of psychiatry and rheumatic fever will be cautious in accepting this last contention.—Ed.]

Neuropsychiatric disturbances appeared in 21 of 23 cases of rheumatic endocarditis studied by Kernohan, Woltman and Barnes: hemiplegia occurred in 10 cases, headache in seven, convulsions in five and chorea in three. There also were instances of twitching of isolated muscles, athetotic dyskinesia, vertigo, syncope, vomiting, fatigue and general weakness. Five patients had psychosis but its relation to the endocarditis of one was not established. Other less severe reactions included delirium, irritability, increased psychomotor activity, emotional instability, insomnia, depression, neurotic behavior and apathy.

[That this was an atypical rheumatic group is indicated by the extraordinary occurrence of hemiplegia 10 times among 23 patients. It also should be noted that the symptoms dis-

cussed by these authors are those of endocarditis and probably not of rheumatic fever per se.—Ed.]

The underlying emotional and psychiatric patterns which tend to govern the formation and expression of symptoms in rheumatic persons were analyzed (Dunbar).

Rheumatic Pneumonia. Nine of Ritchie's 179 patients had signs of so-called rheumatic pneumonia. But Ritchie appeared to question the existence of this disease. Pleurisy occurred in eight cases.

Abdominal Pain. Digilio and Pescatore^{6, 230} continued their studies of pain in the left upper abdominal quadrant on locomotion in cases of rheumatic heart disease. The abdominal pain which is a common manifestation of rheumatic fever among children was described by Taussig: "Usually it is not associated with nausea, vomiting, diarrhea, or constipation, but it may simulate acute appendicitis or peritonitis." In two of 116 rheumatic children, abdominal pain led to error in diagnosis and operation for appendicitis.⁷⁴ Melena was a striking symptom in a case of rheumatic fever in India.²²²

Excessive Fever. This serious manifestation is seldom reported today: it occurred in four of Ritchie's 179 cases; temperatures reached 108 to 109° F. All four cases ended fatally.

LABORATORY DATA IN RHEUMATIC FEVER

Secondary anemia, often severe, develops during active rheumatic fever but disappears as the infection subsides.⁴¹¹ Thus anemia may indicate continued rheumatic activity.

Results of studies of glucose tolerance, catalytic potency of blood, and amounts of glutathione in erythrocytes in cases of rheumatic fever and in controls were not constant and disclosed no relationship of rheumatic fever to hyperinsulinism, scurvy or other metabolic anomalies.^{661, 662, 666}

The formol-gel reaction was compared with the sedimentation rate of erythrocytes as an index of rheumatic activity.^{388, 665} In general the results tended to parallel each other but Schultz and Rose stated that the former differed from the sedimentation rate in that it was positive in rheumatic fever only in the presence of carditis.

[This needs further study; if it is confirmed, the formol-gel reactions would afford important information as to the presence or absence of carditis in rheumatic patients.—Ed.]

DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER

Several papers on the diagnosis of rheumatic fever appeared.^{39, 503, 750, 754, 822} One of the most useful diagnostic measures is the therapeutic test, the response of patients to adequate doses of salicylates.⁷⁵⁴ The differentiation between so-called growing pains and mild rheumatic polyarthritides was already mentioned. The significance of the less striking cardiac physical signs was discussed.⁷⁵⁴ Syngé emphasized the importance of considering

systolic murmurs significant only when accompanied by a definite history of rheumatic fever, cardiac enlargement or diastolic murmurs. Shafar noted the difference between chorea and athetosis of childhood: choreic movements are irregular, jerky, unsustained, and, most important, are not such as might be performed by a normal child; athetosis consists of slow, sinuous, rhythmical movements which blend with one another. The differentiation of juvenile gonococcal arthritis from rheumatic polyarthritis is sometimes difficult.⁷⁹ A specific test for rheumatic fever is badly needed.⁷⁴⁸ In the absence of such, the sedimentation rate of erythrocytes is the most delicate nonspecific index of rheumatic activity.^{30, 252, 303, 754} The formol-gel reaction may also be useful.^{338, 665}

PATHOLOGY OF RHEUMATIC FEVER

General Comment. There has been so much debate as to what should be called an "Aschoff body" that a paper by Aschoff himself defining these lesions is especially valuable; under this term Aschoff includes not only the myocardial nodule but also similar lesions in other organs, e.g., the subcutaneous nodule. He reiterated his belief, also shared by Collins,¹⁷⁷ that the initial tissue change involves the cells; he argued against Klinge's view that fibrinoid degeneration of ground substance is the earliest stage and that cellular changes are secondary. According to Aschoff, myocardial nodules are specific for rheumatic fever.

Heart. Myocardial changes were grouped thus by Ritchie: (1) nonspecific exudative, degenerative and infiltrative processes; (2) abnormalities of mesenchymal cells leading to Aschoff bodies; (3) vascular lesions; and (4) lesions of myocardial fibers. He attributed heart failure not to Aschoff bodies but to nonspecific muscle changes from the "rheumatic toxin" and ischemia. Swift and Cohn likewise stressed the rôle played by rheumatic changes in coronary arteries in causing myocardial weakness. Necropsy in Fernando's 41 cases of rheumatic cardiac disease revealed the coexistence of congenital lesions in three. The incidence of involvement of cardiac valves in Gibson's³¹² 73 cases at necropsy was as follows: mitral, 72 cases, aortic, 46, tricuspid, 41 and pulmonic, 8. Pericarditis was present in 62. Reported was the case of a woman, aged 50 years, who died from severe rheumatic pericarditis and myocardial involvement but had grossly normal valves.¹⁴⁵

Blood Vessels. Italian studies on pathologic changes in large veins and arteries were cited.⁶¹⁴ Lesions in all coats of arteries were noted by Collins.¹⁷⁷ Amorphous fibrinoid material may be deposited in the intima, and later replaced by fibrinous tissue; degeneration may occur in the media, proliferation of connective tissue cells may take place in the adventitia and all coats may be infiltrated with polymorphonuclears, eosinophiles, lymphocytes or plasma cells.

Joints. Studies of synovial tissue^{177, 276} revealed edema, fibrinoid degeneration, proliferation of capillary endothelial cells, slight leukocytic infiltration and foci of proliferated mesenchymal cells. Some of the last were multinucleated, making the lesions resemble Aschoff bodies.

Subcutaneous Nodules. The subcutaneous nodules of rheumatic fever are pathologically similar to myocardial granulomas.^{27, 629} Hart was unable to repeat the observations of Massell, Mote and Jones (1937) who induced the formation of subcutaneous nodules by injecting blood from rheumatic patients into tissues about their own elbows. Hart obtained completely

negative results from 40 rheumatic and eight nonrheumatic children, also from 10 patients with atrophic arthritis and four with Still's disease.

Brain. In one of Ritchie's cases headache and stiff neck developed. At necropsy multiple small (1 to 2 mm.) foci of ischemic degeneration and scattered arterioles plugged with embolic thrombi were found in frontal and parietal lobes bilaterally, but no evidence of meningitis. Another patient who had epileptiform seizures before death, was found to have cerebral edema at necropsy. Kernohan, Woltman and Barnes reviewed the literature on lesions of the nervous system in cases of endocarditis; small embolic cortical lesions were found in 25 of their 26 cases of rheumatic endocarditis. The cardiac disease was considered healed in most instances; thus the embolic lesions were not part of the pathologic picture of rheumatic fever. In bacterial endocarditis the cerebral lesions were larger and more prominent. In brains of rheumatic inmates of a mental hospital Breutsch and Bahr^{111, 112} found obliterating rheumatic endarteritis of small and larger vessels resulting in gross and microscopic infarctions.

Lungs. To Ravenna rheumatic pneumonia was a distinct manifestation with pathologic findings "different from that of any other known disease"; Ritchie doubted the existence of such an entity. Among 179 rheumatic patients were nine who had signs similar to those of "rheumatic pneumonia"; the lungs in two cases which came to necropsy revealed only congestion.

Miscellaneous. Italian work on rheumatic changes in lymph nodes was noted. In Italy some investigators recognize "rheumatic nephritis."⁶¹⁴ Ritchie had one patient, with foci of necrosis to a depth of 2 mm. in the renal cortex.

RELATIONSHIP OF RHEUMATIC FEVER TO OTHER DISEASES

To Atrophic Arthritis. Some physicians regard atrophic arthritis as closely related to rheumatic fever, if not one of its manifestations. Fisher²⁷⁶ considered morphologic changes in joints similar in both diseases, and Kersley described [not very clearly—Ed.] a type of subacute rheumatic infection which tended to "progress to a condition indistinguishable from rheumatoid arthritis." Studies on virus as a possible cause of the two diseases suggested a relationship.^{239, 240, 241} Suspensions of virus-like bodies found in rheumatic exudates were agglutinated equally well by serum from cases of rheumatic fever, of atrophic arthritis, or of other arthropathies. Hence Eagles himself has doubted the significance of these reactions. The histologic changes in subcutaneous nodules in rheumatic fever resemble somewhat (but not fully) those in atrophic arthritis, but this does not prove that the two diseases are the same.¹⁷⁷ Italian workers consider the two diseases distinct.⁶¹⁴

To Exophthalmic Goiter. Rheumatic fever and exophthalmic goiter not infrequently affect the same patient; two such cases were noted by Schultz. Perhaps some underlying constitutional anomaly contributes to the development of both the diseases. Hyperthyroidism may provoke rheumatic activity.²²⁹

To Dermatomyositis. A case of mitral stenosis with dermatomyositis was seen by Kellogg and Cunha; the relationship was probably coincidental.

COURSE, PROGNOSIS AND END RESULTS OF RHEUMATIC FEVER

The prognosis of rheumatic fever must always be considered from the standpoint of the ultimate result as well as that of the immediate attack. Signs and symptoms having a grave immediate import include rapid development of aortic insufficiency, presence of marked cardiac arrhythmia, severe dyspnea and true orthopnea with or without pericarditis, development of marked cardiac enlargement during the attack,⁷⁵⁴ excessive fever, the development of congestive failure, persistence of pyrexia for several weeks, tachycardia persisting after fever has ceased and involvement of the aortic as well as of the mitral valve.⁶²⁹

[If the author meant that the last four suggest the probable development of serious cardiac damage, we agree, but if he meant that these indicate the likelihood of death during the immediate attack, we cannot agree.—Ed.]

Ritchie considered pleurisy a serious rheumatic manifestation, and stated, "The prognosis in these cases is almost invariably grave."

[We take exception to this view; in our experience rheumatic patients with pleurisy have done as well as the average patient.—Ed.]

The data of Massie and Levine indicate that the immediate prognosis is serious in cases of rheumatic fever and pericarditis. The immediate mortality was 16.3 per cent in their 135 cases; but for the patients who survived the immediate attack, the ultimate prognosis was comparatively good, for 36 per cent of 82 patients given follow-up examinations had no evidence of organic heart disease and an additional 14 per cent had only mitral insufficiency.

An excellent follow-up study was made on 1000 rheumatic children seen by Bland and Jones from 1921 to 1936: by 1936, 239 patients were dead, 744 were living and 17 could not be traced. Of the 744 living, 605 (81 per cent) had no limitation of physical activity (312 had no clinical evidence of cardiac damage), 118 (16 per cent) had slight to moderate limitation and 21 (3 per cent) great limitation of cardiac reserve. Forty-eight per cent of those dead died within four years and 68 per cent within six years. These authors found relatively little difference in prognosis regardless of whether the disease began before five years of age, or between six and 21 years. But others^{35, 485} stated that the earlier the age of onset the worse was the prognosis. Of serious prognostic import was the development of marked cardiac enlargement during the initial attack of rheumatic fever.⁷⁷ The severity of individual recurrences was of greater prognostic significance than the number of recurrences. In every fatal case of congestive failure, pathologic evidence of active carditis was found even though clinical evidence was sometimes lacking. Taussig also emphasized the rôle played by recurrent activity of the rheumatic infection in congestive cardiac failure of rheumatic children and in the terminal episode. In general, regardless of the patient's age, the chance of a recurrent rheumatic attack subsequent to a respiratory infection decreases the longer the inactive phase of the disease lasts.⁴²⁹ Of 314 rheumatic children studied by Bland and Jones 25 per cent later presented signs of permanent valvular deformity not present at the time of dismissal from hospital; among two-thirds of these the development of these signs was associated clearly with recurrent rheumatic attacks, and even among the other third indirect evidence suggested that recurrent rheumatic activity had been the cause of the subsequent cardiac damage.

In Russia the younger the child is at his first rheumatic attack, the more frequent the recurrences are likely to be, according to Gornitskaya who found no direct relation between the severity of the first attack and the eventual cardiac damage,

but noted that children who had more than four attacks always were greatly incapacitated. Twelve per cent of his juvenile patients later had normal, 25 per cent considerably reduced, and another 33 per cent markedly reduced functional capacity. Among Gibson's³¹² 1068 rheumatic children who were watched for a number of years, 60 per cent sustained cardiac damage. Polyarthritides occurs more often with carditis than does chorea.^{312, 329} The longer the interval between the causal attack of rheumatic fever and the appearance of obvious mitral stenosis the better the prognosis.⁷⁵⁰

Mortality rates from heart disease in the United States were published (Hedley). Reports of the ultimate prognosis in rheumatic fever based on studies of patients with carditis must be interpreted with caution since they often do not take into account the rheumatic patients who escape cardiac damage. Thus they give information on the prognosis of *rheumatic heart disease* but make that of *rheumatic fever* appear more grave than it actually is.⁷⁴⁸

ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

Factor of Infection. It is agreed that infections, especially of the upper part of the respiratory tract, commonly initiate rheumatic attacks, but it is not agreed that such infections are "specific" provocatives.

Of Ritchie's 100 cases attacks were provoked by such infections in 48, by suppurative appendicitis in two. Among the 749 patients of Jones and Mote respiratory infections (especially sore throats) preceded 58 per cent of the first attacks of rheumatic fever. But the initial rheumatic attack of 37 per cent of the patients began "spontaneously," although in most instances serologic evidence of hemolytic streptococcal infection was found. Approximately half of their patients with inactive disease who acquired "colds" also acquired recurrent rheumatic fever. Of 271 rheumatic exacerbations 67 per cent were associated clinically with respiratory infections, 29 per cent were apparently spontaneous and 4 per cent (12 cases) were associated with trauma or with infections outside the respiratory tract. In another series³⁵ the onset of rheumatic fever apparently was spontaneous in 621 cases, and followed a "chill" (probably tonsillitis), in only 47 instances. Accidents were considered responsible in one case and fright in three.

Rôle of Hemolytic Streptococci. These bacteria are considered the commonest provocative of the disease.⁷³⁵ The prophylactic effect of sulfanilamide seems to support the idea that streptococci cause rheumatic fever.^{163, 761} Studying the significance of prolonged streptococcal antibody formation in rheumatic fever Coburn and Pauli concluded that it indicates continued subclinical activity of hemolytic streptococci. They also reported¹⁶⁵ a precipitin reaction which occurred when serum of patients, withdrawn during the "silent period" after hemolytic streptococcal infection of the throat, was mixed with serum of the same patients obtained a few weeks later after the onset of rheumatic fever. The nature of the reaction was discussed but no definite conclusions as to its significance could be reached.

In eight of nine fatal cases of rheumatic fever hemolytic streptococci were isolated by Green³³⁶ from gross lesions on cardiac valves but not from heart blood; in the ninth case *Streptococcus viridans* was obtained. In five cases from the throat during life were isolated hemolytic streptococci serologically identical with those isolated from cardiac lesions after death. Among 22 nonrheumatic controls, hemolytic streptococci were cultured from valves only twice and in these cases heart blood also

was positive. Green again⁶ discussed³³⁷ the relation of throat infections to rheumatic fever. Antistreptolysin titers were above 100 units in 131 cases of rheumatic fever and below 100 units in 46 control cases. In a histologic study of cardiac valves from rheumatic patients Green found reddish purple, coccoid bodies in gram-stained preparations; whether these were cocci or granules of some sort was not certain, but similar bodies were found in tissues of animals injected with hemolytic streptococci. The results of Green's bacteriologic study of cardiac valves led Collis to report old unpublished results about which he had been dubious: at necropsy in 17 fatal cases of rheumatic fever, hemolytic streptococci were grown from the center of 14 of 15 tonsils, from 13 of 27 cervical or mediastinal lymph nodes, and from 22 of 42 heart valves.

[The work of Green and Collis, if confirmed, will give important support to the hemolytic streptococcus theory. But confirmation is needed.—Ed.]

Other writers²⁷⁰ doubted that streptococci are related to rheumatic fever (or to atrophic arthritis) because the polymorphonuclear reactions usually found in joint tissues in cases of septic arthritis due to hemolytic streptococci are not found in joints of patients with these diseases. Collins¹⁷⁷ considered the histologic findings in rheumatic joints unlike those of any hitherto proved streptococcal disease but thought that this does not exclude the possibility of streptococcal etiology. According to Ravenna "no Italian believes" in a selective affinity of streptococci for joints and heart. Ravenna described experiments in which chronic foci infected with streptococci were produced in rabbits, following which homologous microorganisms were injected intravenously. Focal myocardial lesions were induced but these were found also in hearts of animals receiving injections of various nonbacterial materials and, to a lesser extent, even in normal controls.

Factor of Bacterial Allergy. This theory has been rejected in Italy.⁶¹⁴ Green³³⁷ noted "miniature rheumatic attacks," which he considered allergic phenomena, following subcutaneous injections of hemolytic streptococcal endotoxin. He was "prepared to admit that certain manifestations of rheumatism such as the flitting joint pains may be attributed to allergy," but he could not believe that allergy alone can account for gross changes in tissue. Collins¹⁷⁷ expressed a similar view. But Levinthal staunchly believed in an anaphylactic (not an allergic) mechanism underlying not only rheumatic fever but also various forms of arthritis and gout. [The theoretical reasoning in this paper was ingenious but the data were presented without convincing evidence.—Ed.] Patients with rheumatic carditis were said by Traut and Vrtiak to have asthma, hay fever and urticaria much oftener than normal controls. Pagel also supported the allergic theory.

The cutaneous reactivity of patients with rheumatic fever or Bright's disease, and of controls, to hemolytic streptococcal nucleoprotein, tuberculin and rabbit serum was studied (Schultz).⁶⁶⁴ There were more positive skin reactions to hemolytic streptococcal nucleoprotein among the controls than among the rheumatic patients except for those who had had recent "focal infections." As shown by the development of secondary reactions to rabbit serum, "increased allergic irritability" occurred more often in cases of rheumatic fever or Bright's disease than in control cases. The incidence of this increased allergic irritability was greater among individuals who had suffered recently from focal infections. According to Schultz this is further evi-

dence that alterations in tissue reactivity are associated with rheumatic fever and nephritis.

Virus Theory. Further observations on the agglutination of suspensions of virus-like particles from pericardial and pleural exudates from cases of active rheumatic fever were made by Eagles and Bradley, and Eagles.

The suspensions were tested against serum from 18 patients with rheumatic fever, from 20 with atrophic arthritis and from 16 with other arthropathies as controls. Positive agglutination was obtained in about equal percentages in the three groups (40 per cent, 35 per cent and 42 per cent respectively). There was no consistent relation of agglutination to the clinical stage of disease, and no evidence that it ran parallel to antistreptolysin titers, sedimentation rates of erythrocytes or pyrexia. Attempts to induce disease in monkeys by injecting the suspensions were unsuccessful. Eagles and Bradley questioned whether the so-called virus bodies in rheumatic exudates are true elementary bodies (as in known virus diseases) or are nonspecific bodies that originate in tissue and blood elements arising under abnormal physical conditions of which rheumatic fever is a striking example.

[At the Third International Congress for Microbiology held in New York in September, 1939, Eagles doubted the etiologic significance of these virus-like bodies.—Ed.]

Earlier Italian work on viruses in relation to rheumatism was reviewed by Ravenna who summarized the work of Andrei and himself. They injected whole blood from rheumatic patients into rabbits which were killed three to four weeks later. In 40 per cent they found a widespread endocarditis very similar to that of rheumatic fever, but no myocarditis. But blood from nonrheumatic patients and even milk and horse serum would do the same; perhaps the injected material activated a latent virus in the test animals; in rheumatic fever a virus may be active but only in symbiotic association with streptococci.

"Pleuropneumonia-like microorganisms" were apparently recovered by Swift and Brown from the articular exudate of a patient with rheumatic fever, and from chorio-allantoic membranes inoculated with rheumatic exudates and from "pneumonic lungs" of similarly inoculated mice.

[But at the Third International Congress for Microbiology, Swift and Brown stated that what they originally thought were pleuropneumonia-like microorganisms from rheumatic exudates were either artefacts or microorganisms recovered from the inoculated mice and not related to rheumatic fever.—Ed.]

Vitamin Deficiency. No support was given to the theory of vitamin deficiency.

Factor of Trauma. Trauma plays a secondary, but important, rôle. In needleworkers and laundresses joints of hands and arms tend to be involved early; valvular lesions and subcutaneous nodules tend to develop at sites subjected to local trauma.⁷⁴⁸

TREATMENT OF RHEUMATIC FEVER

Rest. This is the all important remedy in active rheumatic fever.^{35, 252, 363, 440, 740, 748, 750, 754} Complete rest in bed is essential in the presence of persisting infection. Sundell favored a cautious trial of sitting up despite occasional slight fever if all other signs are favorable. When the patient is allowed out of bed, the resumption of normal physical activity must proceed

slowly; first gradually increased time in a chair, then cautiously increased walking on the level, finally climbing of stairs and other activity. Convalescent care is important.^{35, 440, 748} Needed are more institutions for the sanatorium care of rheumatic convalescents.^{364, 748} Although rest is vital in cases of active rheumatic fever, it is not indicated for those of inactive rheumatic heart disease unless definite cardiac decompensation is present.^{252, 702, 750} The important factor in inactive rheumatic disease is not rest but the avoidance of a recurrence of the active infection. There is danger of inducing cardiac neurosis by enforcing unnecessary rest on patients with inactive rheumatic heart disease simply because of the presence of murmurs.⁷⁰²

Drugs. 1. Salicylates. The effect of salicylates, aminopyrine and other "antirheumatic" drugs on the symptoms of rheumatic fever is great, but these drugs have no effect on the heart.^{503, 629, 740, 750, 822} Taussig recommended the auxiliary use of alkali if over 30 grains of salicylates are given in 24 hours. Magnesium carbonate or oxide was the alkali of her choice because of its synergistic action with salicylates in relieving pain. According to her, salicylates relieve precordial and abdominal pain in rheumatic fever.

[These drugs seem to relieve some abdominal pains but not others, depending on their underlying pathologic basis, i.e., exudative inflammation, subperitoneal hemorrhage, arteritis, etc.—Ed.]

Aminopyrine has six times the potency of salicylates as an antirheumatic drug but must be used with caution because of the danger of agranulocytosis.⁷⁵⁴

2. Digitalis. Although the great value of digitalis in relieving congestive cardiac failure and auricular fibrillation in inactive rheumatic heart disease was recognized, some^{252, 750, 754} considered its use dangerous in the presence of active carditis.

[To avoid toxic effects digitalis should be given cautiously in cases of rheumatic carditis with prolonged P-R interval, but it is unjustifiable to withhold it, in the face of congestive heart failure and auricular fibrillation, just because the patient has rheumatic activity.—Ed.]

3. Sulfanilamide. Two papers confirmed previous reports that sulfanilamide is not beneficial but may be actually harmful in the treatment of active rheumatic fever^{163, 629} or when given in the "silent period" after the onset of a precipitating sore throat.¹⁶³ The prophylactic value of this drug is discussed later.

4. Other Drugs. Arsenic for Sydenham's chorea was considered useful by some^{613, 655} but not by others.²⁵² [We agree with the latter.—Ed.] Quinidine can be used for children according to the same principles governing its use for adults.³⁴⁵ Elghammer was "astonished over the good results sometimes obtained from the use of glucose intravenously during the period of decompensation of the heart."

Removal of Infected Foci. Some writers^{252, 750} considered tonsillectomy dangerous during a rheumatic attack and stated that if it is to be done, all signs of rheumatic activity should be gone. Rheumatic children have more marked changes in sedimentation rates and more loss of weight following

tonsillectomy than do nonrheumatic children.³¹ But infected tonsils should be removed.⁵⁰³ Data of Bach and his co-authors indicated that although tonsillectomy before the onset of rheumatic fever does not decrease its incidence, severe cardiac damage was 8.7 per cent less frequent among children whose tonsils had been removed before the onset than among those not subjected to the operation.

Vaccines: Serums. Nothing was reported thereon.

[This is an index of their ineffectiveness.—Ed.]

Fever Therapy. Of 20 patients with Sydenham's chorea given artificial fever by Elkins and Krusen eight obtained complete clinical remissions; seven others, slight to marked improvement. Having treated 70 choreic patients, E. L. Bauer concluded that artificial fever therapy not only stops the choreic attack but also lessens the number of recurrences of rheumatic fever and the extent of cardiac damage. Simmons and Dunn treated 31 rheumatic patients: six of the nine patients with joint pain obtained prompt relief, the remaining three less prompt relief. In 15 of 20 cases the sedimentation rate of erythrocytes fell sharply. Fever therapy was considered by some^{154, 269} of value not only for chorea but for the carditis also. But other physicians disagreed.^{35, 252}

[The use of fever therapy for rheumatic manifestations other than chorea should be considered experimental.—Ed.]

Diet and Vitamins. Some physicians^{32, 530} recommended a diet such as would be suited to any febrile disease. Jones and Taylor found that vitamins B (300 international units), C (2000 international units), A (13,000 international units) or D (2370 units), given daily from February to June were not of any curative or preventive value to rheumatic children.

Miscellaneous. The effect of heliotherapy was not marked, but was pleasing to children so treated.³⁵ "Improvement" was obtained by 17 of Poulton's 26 rheumatic patients treated in an oxygen tent for from one week to 82 days.

PREVENTION OF RHEUMATIC FEVER

Prophylactic Value of Sulfanilamide. Two important papers concerned the use of sulfanilamide in the prevention of hemolytic streptococcal infections of throat and the subsequent attacks of rheumatic fever. To 80 children with inactive or quiescent rheumatic fever Coburn and Moore gave 2 to 3 gm. of the drug daily, in three doses, for four to eight months: 79 escaped hemolytic streptococcal infections and signs of rheumatic activity; only one child had a respiratory infection followed by a vague illness which may have been atypical rheumatic fever. Thomas and France carried out similar studies on 30 juvenile and adult patients. The dosage was 15 to 20 grains (1 to 1.3 gm.) daily for seven months each in the winters of 1936 and 1937. None of the rheumatic patients receiving sulfanilamide had hemolytic streptococcal infections or rheumatic attacks, whereas four of 30 control rheumatic patients, not given the drug, underwent five major attacks

of rheumatic fever during the same period. None of these patients had to discontinue the drug permanently on account of symptoms of toxicity; but some of those treated by Coburn and Moore had to do so.

[The importance of these studies can scarcely be exaggerated if the results are borne out by further work.—Ed.]

Other Measures. A course of salicylates given for one week every month helps prevent rheumatic recurrences according to E. L. Bauer. [Most American workers would not agree, nor do we.—Ed.] The value of certain general measures for preventing rheumatic fever and carditis was stressed,³⁷³ such measures as improved living conditions, prolonged convalescent care, better and earlier case finding by school health officers.

Public Health Aspects. Rheumatic fever is one of the major American public health problems.³⁷³ It should be a reportable disease⁷⁴⁸ as it is in Italy.⁶¹⁴ In Philadelphia during 1936 rheumatic heart disease was exceeded only by tuberculosis, lobar pneumonia and syphilis as a cause of death; it caused more deaths of persons under 20 years of age than whooping cough, measles, meningococcal meningitis, diphtheria, scarlet fever and poliomyelitis combined.³⁷³ Rheumatic fever and rheumatic heart disease have been neglected greatly by health authorities; more furore is raised over one case of leprosy than over 100 cases of rheumatic fever. Facilities for the proper care of rheumatic cardiacs are woefully insufficient in the United States.⁷⁴⁸ In view of the cost of keeping such patients in general hospitals, the problem could be solved more economically by providing suitable sanatoria where the cost per patient would be lower and problems peculiar to rheumatic fever could be more carefully studied.⁷⁴⁸ Plans for the care of rheumatic school children were reported.^{364, 440, 663} The rôle of the social worker and psychiatrist is important; the diagnosis should be made early enough in life so that victims can be rehabilitated and taught trades within the probable limits of their future physical capacities.

"Every rebuilding scheme, every slum destroyed, every new hygienic school built, every playing field provided, every increase in the standard of living, every improvement in the knowledge of nutrition, helps to decrease the incidence of acute rheumatism."³²²

The London County Council's Rheumatism Scheme was described.³⁵ This comprehensive plan for the supervision of rheumatic children under 16 years of age has five general aims: (1) gradual amplification of special rheumatism units until there are enough beds to provide for an average period of treatment of six months for all children with active rheumatic fever; at the time of the report, 650 beds were available for acute and subacute cases, and 250 more for doubtful or very mild cases; these units are recognized by the Board of Education as "hospital schools" and staffed by qualified teachers; (2) establishment of "rheumatism supervisory centers" for early diagnosis and supervision of quiescent cases; 21 were in operation in December, 1938, handling 5160 children; (3) establishment of an alternative system of supervision by school physicians; (4) investigation of the child's home environment by special workers; unsatisfactory conditions are reported to the Borough Medical Officer of Health; (5) central coördination of various branches of the scheme.

In addition to these facilities provided by the London County Council there are in London 467 beds in voluntary children's hospitals and 233 beds in "heart homes" and hospital schools other than those of the Council's units, also out-patient facilities and beds in hospitals not especially for children. The medical supervision, treatment, and special education of rheumatic children costs the city of London about \$1,000,000 yearly; despite this about 20 per cent of the children sustain enough cardiac damage to render them unable to be self-supporting after leaving school.³⁵

ERYTHEMA NODOSUM

Erythema nodosum is considered by some a common, by others a rare, accompaniment of rheumatic fever. The view that it is a nonspecific skin reaction which may occur with different infections received support from a study of acute coccidiosis among children by Faber and associates.

Acute coccidiosis is an acute febrile disease caused by the fungus *coccidioides immitis* and is characterized by initial systemic symptoms not unlike influenza. It is often followed by erythema nodosum and accompanied by specific sensitivity to the products of the fungus. The disease has long been known in the San Joaquin Valley, California, but sporadic cases have been noted elsewhere. The mortality rate of coccidioidal granuloma is 50 per cent; the acute form has caused but one death in 700 cases. It is common among children, and in 22 of the 24 cases noted, typical lesions of erythema nodosum were present. In nine of these, acute arthritis was noted also and involved knees and ankles, in one case a shoulder. The joints were tender to pressure and painful on motion but not red. Diagnosis was established by skin testing with 0.1 c.c. of a 1:1000 solution of coccidioidin. No specific therapy is available.

The connection between erythema nodosum and tuberculosis was discussed.^{350, 699, 763} Thompson⁷⁶³ regarded erythema nodosum as a sign that the host had developed resistance (immunity) as well as skin hypersensitivity (allergy).

Erythrocyturia was observed by Wallgren in every third or fourth case of erythema nodosum among 88 children. The phenomenon was considered similar to capillary fragility.

CHRONIC ARTHRITIS: THE TWO COMMON TYPES

No new statistics on the incidence of the two great types of chronic arthritis (atrophic and hypertrophic) were reported.

Relationships. The orthodox differentiation of these two types was given.^{51, 542, 628, 801} It is often said that atrophic and hypertrophic arthritis are expressions, at opposite ends of the same scale, of a single disease. Having studied their comparative pathology Collins¹⁷⁸ emphatically disagreed with this idea. According to him they are totally different diseases even though secondary hypertrophic changes may occur late in the course of atrophic arthritis. It is commonly [but erroneously—Ed.] believed that persons with atrophic arthritis are usually tall and thin, those with hypertrophic arthritis shorter and stout. The mean height of Weber's 64 patients with atrophic arthritis was 68.1 inches, the mean weight 146 pounds;

the mean height of his 21 patients with hypertrophic arthritis was 67.8 inches, the mean weight 162 pounds.

[To him this difference was "impressive"; to us it is not. The average age of the latter group was eight years more than that of the former.—Ed.]

ATROPHIC (RHEUMATOID, PROLIFERATIVE, INFECTIOUS) ARTHRITIS

Influence of Age and Heredity on Incidence. In Monroe's 267 cases the disease began at an average age of 32 years, before the age of 10 years in 3 per cent, after the age of 60 years in 2 per cent. About 20 per cent of his patients gave a history of atrophic arthritis or of rheumatic fever in parents or siblings.

General Clinical Data: Symptoms and Course of Atrophic Arthritis. The disease was, as usual, divided by some writers^{51, 207, 410} into two varieties or species: (1) "primary" or "typical" atrophic (or rheumatoid) arthritis, and (2) "active infective," "atypical" or "secondary atrophic" (or rheumatoid) arthritis. [These have been described in previous Reviews.—Ed.] Under the term "subacute rheumatic infection" Kersley described cases of young adults, many of whom had had rheumatic fever, chorea or growing pains, who later had transient articular pains and swellings without notable anemia or increased sedimentation rates; some had "a tendency for slight fusiform swelling of the joints to persist and slight contractures to occur merging into a rheumatoid or periarticular fibrositic syndrome."

[His data were insufficient to clarify the vague term used.—Ed.]

Clinical details in two new series of cases were reported. In 52 per cent of Weber's 64 cases the disease began acutely. The following joints were affected: knees in 64 per cent; ankles in 33 per cent; hips in 32 per cent; spine in 30 per cent; feet in 28 per cent; shoulders in 25 per cent; wrists in 23 per cent; hands in 19 per cent [an unusually low incidence in hands—Ed.]; elbows in 6 per cent; jaws in 2 per cent. Subcutaneous nodules were present near elbows in 3 per cent, on fingers in 6 per cent. Functional cardiac murmurs were present in 22 per cent of cases; organic cardiac lesions were found in none.

Of Monroe's 267 patients whose average age was 39 years and whose "arthritic age" averaged seven years, 30 per cent were overweight (average 32 pounds), 41 per cent were of normal weight, 28 per cent were more than 20 pounds underweight. "Ten to fifty per cent of the original body weight may be lost within a few months." Joints affected were in the fingers in 70 per cent of cases, knees in 54 per cent, ankles in 52 per cent, wrists in 48 per cent, lumbar vertebrae in 35 per cent, elbows in 34 per cent, shoulders in 34 per cent, thoracic vertebrae in 26 per cent, hips in 26 per cent, sacro-iliac joints in 20 per cent, toes in 14 per cent, jaws in 4 per cent, sternoclavicular joints in 0.5 per cent. [Note that in this series hands, wrists and elbows were affected much oftener than in Weber's series, feet less often.—Ed.] In Monroe's cases "valvular heart disease" occurred in only 4 per cent, hypertensive and arteriosclerotic heart disease in only 5 per cent. A clinical chart for chronic arthritis was devised.³⁵⁴

ATROPHIC ARTHRITIS: SPECIAL CLINICAL FEATURES

Effect of Toxic Hepatitis and Jaundice from Cinchophen. Another example of the beneficial effect of toxic hepatitis and jaundice on atrophic arthritis, even though of long standing, was reported.

Lichtman saw a man, aged 47 years, who had had painful knees for 10 years. The pain at night was so severe that he "could not cross his knees in bed and was compelled to assume unusual postures to avoid pain." After taking 15 grains of cinchophen daily for a few days he developed generalized pruritus and later painless jaundice with greenish brown stools. Icterus index was 27 units, serum bilirubin 4.5 mg. per cent, van den Bergh reaction positive. Blood cholesterol was 355 mg. at first, 250 mg. per cent two weeks later. "The patient noted from the very onset of his jaundice that he was completely free of the pains in his knee joints with which he had suffered persistently over a period of ten years." Within six weeks the jaundice disappeared: "with the disappearance of jaundice the joint pains returned."

[Roentgenograms did not reveal any changes in knees after 10 years of illness therein; despite this Lichtman believed that atrophic arthritis was present. A week after the pains returned to the patient's knees stiffness of fingers also developed.—Ed.]

Of interest in this connection is the observation of Boots that patients with atrophic arthritis frequently present redness of the thenar and hypothenar eminences of the hands, similar to the "liver palms" of patients with cirrhotic livers. The finger tips may show this same redness. Perhaps the liver is involved in both of these conditions. This so-called liver palm is also seen sometimes in peripheral vascular disease.

Effect of Urticaria (without Jaundice) Produced by Cinchophen. Under certain conditions actual jaundice is not necessary for the appearance of the phenomenon just mentioned. Complete relief of arthritic symptoms may occur following urticaria from cinchophen toxicity without jaundice.

In 1933 Hench reported a case of atrophic arthritis with complete cessation of pain following urticaria which arose after cinchophen administration but which appeared six weeks before the onset of visible jaundice. Rawls⁶¹⁵ has confirmed this observation. In studying the relation of cutaneous sensitivity, hepatic function, leukopenic index and toxic effects from cinchophen he noted the onset of urticaria from cinchophen toxicity in nine cases. Jaundice occurred in none, but in five cases notable amelioration of arthritic symptoms occurred. With the onset of urticaria in three cases or just after its disappearance in two cases there was marked diminution of articular pain, tenderness, swelling and stiffness: relief was complete in three cases, almost complete in two cases and lasted from five weeks to five months. The relief was proportional to the severity and duration of the urticaria and was "far more striking than that obtained with cinchophen per se."

[Obviously in cinchophen toxicity several different chemical reactions occur: that which relieves articular symptoms is not the one which produces urticaria; also it appears that actual hyperbilirubinemia is not necessary for the relief of joints.—Ed.]

Effect of Pregnancy. During pregnancy joint pains are almost always definitely less "due to the fact that glandular activity is stimulated and resistance to infection is at its best; after childbirth when such stimulation has subsided there is frequent exacerbation of joint symptoms" (Burbank). In contrast to the relief of atrophic arthritis by pregnancy is the pelvic osteoarthropathy that may develop during pregnancy in nonarthritic women (Young).

Ocular Lesions Complicating Atrophic Arthritis. In about 2.5 to 4.5 per cent of cases of atrophic arthritis iritis develops according to Berens, Angevine, Guy and Rothbard. Ocular lesions (iritis, cyclitis, uveitis) which may complicate atrophic arthritis or spondylitis were described by Juler.

Attacks generally last two to six weeks (unless the ciliary body is affected) and often recur. Treatment includes local therapy for eyes, removal of infected foci (even of questionable foci in recurrent cases) and protein shock therapy with milk or typhoid vaccine.

PATHOLOGIC CHARACTERISTICS OF ATROPHIC ARTHRITIS

Synovial Membrane. There are two chief microscopic synovial lesions in atrophic arthritis: (1) regions of fibrinoid degeneration surrounded by a corona of fibroblasts; Fisher⁵ considered these lesions similar to those of rheumatic fever and many now regard them as the primary and perhaps the specific tissue change in "rheumatism"; (2) large follicle-like collections of lymphocytes or plasma cells; these are considered specific for atrophic arthritis by some,⁶ but not by others. According to Collins¹⁷⁷ neither of these lesions is specific: fibrinoid swelling of collagenous connective tissue appears under certain non-specific stimuli whether or not tissues are hypersensitive; the large foci of round cells probably represent a nonspecific synovial reaction to any chronic inflammation. Collins presented an unpublished microphotograph of W. E. Swift showing similar collections of lymphoid cells in synovial villi of a tendon sheath in a case of chronic traumatic tenosynovitis without evidence of atrophic arthritis or rheumatic fever. [Could the patient have been developing early atrophic arthritis? A follow-up note on this case would be interesting.—Ed.] Late in atrophic arthritis secondary osteo-arthritic changes may occur.¹⁷⁸

LABORATORY DATA IN ATROPHIC ARTHRITIS

Roentgenograms. No new data were presented.

Hemoglobin, Cell Count and Hematocrit. A moderate hypochromic anemia was present in many of Monroe's 267 cases: in 25 per cent values of hemoglobin were between 50 and 70 per cent; erythrocyte counts ranged from 3,500,000 to 4,200,000 per cubic millimeter. During acute exacerbations leukocytosis (generally 9,000 to 13,000, rarely over 18,000 cells per cubic millimeter) often occurred. Collins, Gibson, Race and Salt considered hematocrit estimations of packed red cell volume easier to do routinely and more informative than erythrocyte counts. Information concerning erythrocytes (degree of anemia in terms of volume of erythrocytes), leukocytes (depth of leukocyte cream) and plasma (presence of subclinical icterus) can be obtained thereby.

The mean percentage of nonfilamented leukocytes in Stiles' 14 cases was 36.9 (normal 7 per cent or under).

Sedimentation Rates. Yeoman noted changes in sedimentation rates in 40 cases after a course of spa therapy alone or with chrysotherapy, female sex hormones or typhoid vaccine. Improvement in sedimentation rates occurred in most of the patients treated by spa therapy alone. Improvement in rates generally (but not always) paralleled clinical improvement.

Other papers on sedimentation rates discussed the history of the test, comparisons of various methods, and the factors which influence the results.^{356, 424, 504, 637} Chief factor regulating erythrocyte sedimentation is fibrinogen according to some, globulin according to others. Ropes, Rossmeisl and Bauer found no absolute correlation between rates and the plasma protein fractions. They concluded that "variations in rates are due to variations in the colloidal state of plasma with consequent changes in the electric charges on the proteins and red cells. Variations in the concentration of fibrinogen, globulin and other constituents affect the rate through their effect on the colloidal state of plasma." Ham and Curtis also noted that the rate may fail to correlate in a linear manner with fibrinogen when the serum globulin is elevated or erythrocytes are notably altered in size.

In view of the effect of pregnancy on atrophic arthritis the following data are of interest. During pregnancy the plasma volume increases and produces hydremia which may be correlated with an increase of globulin.³¹⁰ The sedimentation rate increases during pregnancy⁴²⁴ from the tenth or twelfth week and does not become normal until three or four weeks postpartum (Wintrobe, 1937).

[The period when rates are elevated corresponds closely with that during which the ameliorating effect of pregnancy is usually noted.⁶—Ed.]

Normal values for sedimentation rates in different age groups were established by Osgood and colleagues. No significant sex differences were noted; a sedimentation rate of 15 mm. at the end of 45 minutes (Westergren method) was considered the upper limit of normal. The Westergren method was regarded by many as the simplest and most reliable.^{360, 573} Others described "simpler" methods: that of Brooks involved the use of a venipuncture needle on the end of the marked pipette used for the test; this allows the pipette to be filled directly from the vein and then to be set vertically in a holder. Goldberger's "rapid bedside test" involved the use of unspread blood films on slides: characteristics of the cellular meshwork depend directly on the sedimentation rate. More elaborate and presumably more accurate tests were described.^{209, 560} Collins, Gibson, Race and Salt favored a wide-bore tube method using oxalated blood and permitting correction of the result to a standard erythrocyte volume. Their method is used in the four largest British hospitals for rheumatic diseases. As an anticoagulant they preferred oxalate to citrate which may retard the rate. But others considered citrated blood more stable; oxalated blood must be tested within the hour.^{65, 360, 667} Some workers concluded that the correction of sedimentation rates for anemia gives results which are more often misleading than helpful,³⁶⁰ but others considered such correction generally necessary.³⁴³

To avoid one of the complicating factors (fibrinogen) Coke developed his differential serum sedimentation test.^{172, 173, 174, 207} It is a modification of Bendien's test for cancer. Characteristic curves were noted for fibrositis, atrophic arthritis, "infective arthritis," osteo-arthritis and "spondylitis adolescens." Coke and Crowe considered this test useful in controlling gold or vaccine therapy to avoid toxic reactions. Gibson³¹⁰ considered it useful but not favored in England. According to Shackle much more work is needed to establish the claims made for it: "It is doubtful if it has any affinities with the [erythrocyte] sedimentation rate at all."

Blood Chemistry. Serum proteins in 75 cases of atrophic arthritis (48 "severe," 27 "moderate") were studied by Scull, Bach and Pemberton. Average values for total protein were essentially normal; those for serum albumin were normal or slightly subnormal, those for serum globulin, normal

or somewhat elevated; thereby a reduction was produced in the albumin-globulin ratios. Deviations were not diagnostic.

[The classification of the arthritides used in this paper is confusing and represents quite a departure from that previously used by the same authors. They have included as "rheumatoid diseases" not only atrophic arthritis and spondylitis but also hypertrophic, syphilitic, tuberculous and even gouty arthritis. To add to the confusion, an additional undefined group of "miscellaneous rheumatoids" was included and no definition of the "non-rheumatoid controls" was given. Rheumatologists are trying to establish a precise, universally understood meaning for the (synonymous) terms "atrophic and rheumatoid." The indiscriminate broadening of the meaning of the term "rheumatoid disease" as in this report is regrettable.—Ed.]

In 68 per cent of the 50 cases of Rawls, Weiss and Collins values for serum albumin were subnormal, i.e., less than 4.5 mg. per 100 c.c. of serum (actual figures were not given). There was an abnormal albumin-globulin ratio (under 2) in 38 (76 per cent) of the 50 cases: ratios were 2 to 2.8 in 12 cases; 0.6 to 1.8 in 38 cases. These results with other data supported the idea that hepatic dysfunction often occurs in atrophic arthritis.

Concentrations of serum phosphatase studied by Steinberg and Suter were about normal (average normal 3, upper limit of normal 4.2 Bodansky units) in 44 cases of atrophic arthritis regardless of the degree of involvement, stage of disease or age of the patient, except that prolonged disease tended to lower the phosphatase content. Values ranged from 1.6 to 2.8 (average, 2.3) units. A point of diagnostic significance to be recalled is if a patient with atrophic arthritis presents an elevated value for serum phosphatase, suspect some coincident bone disease, e.g., malignancy or osteitis deformans. [An important point.—Ed.] Values were also normal in hypertrophic arthritis. These results agreed essentially with those of Smith, Klein and Steck. They considered as normal 1.5 to 4 units; in their 18 cases of atrophic arthritis the average value for serum phosphatase was 2.69, lowest 0.44, highest 5.40 units. The daily use of massive doses (150,000 to 400,000 units daily) of vitamin D tended to decrease the serum phosphatase. Similar results before and after such therapy were also seen in cases of hypertrophic arthritis.

Glucose tolerance tests gave normal results (blood sugar 80 to 130 mg.) in all of 11 cases studied by Weber. Liver function tests will be noted under "Etiology and pathogenesis: hepatic dysfunction."

Synovial Fluid. In acute atrophic arthritis the O_2 tension of synovial fluid is higher and the CO_2 tension is lower than normal, perhaps because of some "interference with the blood and/or lymph supply to the joint" (Savage and Taylor). The vital azo dye, T-1824, or Evans blue, when injected intravenously combines with serum proteins to form a large molecular aggregate which cannot pass through uninjured, but does pass through injured, capillary endothelium. Burman and Kling injected it intravenously in five cases of atrophic arthritis; in all cases it appeared in synovial effusions. Measuring the concentration of the dye in synovial fluid may give an index to the activity of synovial inflammation in a given case: the more acute the arthritis, the greater the concentration of the dye in synovial fluid.

[But the sedimentation rate of erythrocytes is a much handier and probably more accurate index of the degree of inflammation.—Ed.]

Basal Metabolic Rates. These will be noted under "Etiology and pathogenesis: factor of endocrine abnormality."

ETIOLOGY AND PATHOGENESIS OF ATROPHIC ARTHRITIS

Factor of Infection. No new data of significance were reported to support or refute the infectious theory.

1. *Foci.* A wide divergence of views regarding the importance of septic foci is held in America and Europe. In the United States opinion is apparently less unanimous than it is in Germany where much importance is attached to such foci.⁷⁵⁷ Gingivitis was considered more important than periapical infection by Cogan and demands special dental therapy, not just "cleaning." Monroe, however, considered gingivitis unimportant and root abscesses (present in less than 10 per cent of his cases) "greatly overrated as a source of arthritis." To him infected tonsils seemed more important. Infected teeth and tonsils were present in 75 per cent of Weber's 64 cases. Infected sinuses, including "silent sinusitis," have been considered by some^{1, 5} to be commonly present in cases of atrophic arthritis. Hamblen-Thomas noted sinusitis among 18 to 60 per cent of "chronic rheumatic patients" referred to him in different years. [Doubtless the incidence was high because probably only patients with suspected sinusitis were referred to him, a nose and throat specialist.—Ed.] Others (e.g., Anderson, 1930) rarely found sinusitis among arthritics. It was present in 5 per cent of Monroe's cases. Williams and Slocumb found roentgenographic evidence (cloudiness) of sinusitis in 42 of 100 cases of atrophic arthritis, but sinusitis was clinically active in only 20 cases. In one of these 20, roentgenograms did not give evidence of sinusitis.

Infections of prostate, female pelvis, gall-bladder and intestines rarely cause arthritis, according to Monroe, but Fishbaugh frequently incriminated the colon: in 80 of 140 cases of "chronic arthritis" [type unstated—Ed.] articular symptoms waxed and waned with intestinal symptoms. Constipation made the joints worse; "starvation" (undefined) lessened articular pain and swelling. [The temporary relief of articular pains which catharsis sometimes produces may result from the removal of water from the body, according to some workers.—Ed.] Present were fermentation of stools in 118, colonic stasis in 140, diverticulosis in 23 cases. According to Meyer: "Infections in veins, and not in diseased teeth and tonsils, are the most prevalent focal infections and therefore, the most frequent cause of rheumatism." He allegedly found "latent phlebitis" of the legs and "latent jugular phlebitis" in "nearly every rheumatic condition." "Jugular phlebitis is the missing link between oral infection and rheumatism."

[No proof for these statements was given and they are contrary to our experience.—Ed.]

A summary of Rosenow's numerous studies on the relation of streptococci to focal infections and on the characteristic cataphoretic velocity and elective localizing power of these bacteria in cases of chronic atrophic arthritis was reported. By studying the precipitation reactions of the serum of patients and the serum of horses hyperimmunized with the streptococci,

and the erythematous reactions to intradermal injections of euglobulin fraction of antistreptococcal serum, Rosenow obtained what he considered to be serologic proof of the specificity of the streptococci isolated.

2. *Blood Cultures.* Studies of blood cultures seemed "useless" to Shackle. But Traut who found pleomorphic bacteria in the blood in 71 per cent of his cases of "chronic arthritis" stated his belief that many of the "different" bacteria recovered by various workers may have been mutations of one organism. Dissociation of Traut's organism occurred especially in the blood of patients with chronic, but not with acute, alcoholism. The dissociating factor was independent of the amount of alcohol in the blood. But the blood of guinea-pigs made alcoholic for five weeks did not cause the tested bacteria to dissociate.

3. *Joint Cultures.* Aerobic cultures of synovial fluid in about 80 cases were "invariably sterile" (Collins). Synovial fluid is highly bactericidal; "Can we be sure that joint *tissues* in the early stages of the disease are always sterile?"

4. *Agglutination Tests.* For the first time in several years no new studies were reported thereon. They were considered "of doubtful significance" ⁶⁷⁶ and not of sufficient value to be done routinely.⁵¹

5. *Precipitin Tests.* No data thereon were reported except those by Rosenow just noted. In 67 per cent of 12 cases of atrophic arthritis the serum gave positive precipitation reaction to the serum of horses hyperimmunized with "arthrotropic streptococci"; in 50 per cent, to serum of horses immunized with "encephalitis streptococci"; in 0 to 8 per cent, to serum of horses immunized with streptococci from other diseases. Bauer⁵¹ considered streptococcal precipitin tests of little diagnostic value.

6. *Antistreptolysins.* No new data were reported. Estimations gave titers "too variable for value." ⁶⁷⁶

7. *Antifibrinolysins.* No data were reported.

[Apparently investigators are getting as discouraged in interpreting indirect serologic evidence as they are in evaluating the direct cultural evidence of the infectious nature of this disease.—Ed.]

8. *Skin Tests.* In 42 cases Rosenow noted that the erythematous reaction to intradermal injections of the euglobulin fraction of various antistreptococcal serums was much larger against the euglobulins prepared with streptococci from cases of arthritis than against those from any other cases. Skin tests with filtrates from various bacteria isolated from different foci were used by Anderson, Lamb, Barrett, and Nerb to determine which filtrates should be used to "desensitize" patients. The commonest organism considered responsible was an alpha (green producing) streptococcus from stools. All of Reeves' [unstated number of] cases of atrophic arthritis demonstrated cutaneous hypersensitivity to streptococcal antigens: in a third the reaction was only to indifferent streptococci, in a third only to *Streptococcus viridans*, and in a third to all of three antigens (from *Streptococcus viridans*, hemolytic, and indifferent streptococci).

9. *Complement Fixation Tests.* No data were reported.

Theory of Bacterial Allergy. This theory was favored by several.^{203, 385, 483, 621} Hicks and Wyatt employed a "specific leukopenic index to streptococci" to uncover evidence of streptococcal allergy and to measure the amount of desensitization accomplished in cases of atrophic arthritis by means of streptococcal vaccines given intravenously.

Vaughn (1934) fed patients test foods on a fasting stomach and noted subsequent variations in leukocyte counts at four half-hour intervals. Ordinary leukocytosis followed the ingestion of food to which the patient was not allergic, but leukopenia followed the ingestion of food to which the patient was known to be highly sensitive. Ishmael (1937) noted that leukopenia similarly follows the intravenous injection of small amounts of a streptococcal substance in cases of atrophic arthritis. Hicks and Wyatt noted that in normal control cases and in cases of hypertrophic arthritis leukocytosis followed the intravenous injections of a streptococcal protein and in cases of atrophic arthritis it followed the intravenous injection of a substance from *Staphylococcus aureus* and *Bacillus typhosus*. But in the cases of atrophic arthritis, when the streptococcal protein was used, leukopenia always resulted. In 34 such cases the leukopenia ranged from 15 to 52 per cent and averaged 31 per cent. Hence the degree of leukopenia produced was used as a gauge of the sensitivity, to streptococci, of a given patient with atrophic arthritis. A course of vaccine given intravenously diminished the average leukopenia by about 50 per cent, i.e., it "diminishes the allergy" by about 50 per cent. These results were considered "major evidence that the essential etiology of atrophic arthritis is a combination of streptococcus focal infection coupled with induced or constitutional hypersensitivity to the protein of this organism. In other words, the host factor is streptococcus allergy."

Discarding the term "allergy" because of its vagueness Levinthal considered that all the rheumatic diseases represent "anaphylactic reactions." Space does not permit an adequate synopsis of his concept; the original reference should be consulted.

[This is an interesting but a hypothetical paper with few data to support the writer's ideas. It should be read in connection with that of Pagel in which the probably allergic nature of rheumatic granuloma and their relationship to the epithelioid cells of tubercles are discussed.—Ed.]

According to Monroe, Traut and Vrtiak patients with atrophic arthritis are no more subject than nonrheumatic persons to the commoner well-recognized allergic diseases, asthma, hay fever and urticaria.

[The conclusion of Traut and Vrtiak seems at variance with their tabulated data which indicated that allergic diseases were less frequently associated with atrophic arthritis than with hypertrophic arthritis or rheumatic heart disease but were still more frequent than among patients used as controls. The percentage incidence of various diseases in 100 cases used as controls and in 175 cases of atrophic arthritis respectively was: asthma 2 and 5.2; hay fever 1 and 12.6; urticaria 13 and 21; eczema 5 and 8; rhinitis 14 and 25; migraine 18 and 36. In other words these diseases were generally about twice (hay fever about 12 times) as frequent among the arthritics as among the controls.—Ed.]

Virus Theory. Eagles discussed further the isolation by himself and his colleagues^{5, 6} of virus-like bodies from the exudates of patients with atrophic arthritis (and rheumatic fever), their agglutination by the patients' serums but their failure to produce rheumatic lesions in monkeys.

Dyson found no bacteria in synovial fluid in a case of "multiple arthritis of some duration with deformities," but when the fluid was injected intraperitoneally into a guinea-pig, a delayed fatal pericarditis occurred. Injections of the pericardial fluid into other guinea-pigs also produced a similar reaction. A pneumococcus type 19 was finally recovered but since this organism does not produce such delayed lesions in guinea-pigs, Dyson suggested that a virus was present in the original synovial fluid.

Factor of Trauma. The rôle of chronic postural trauma in the production of chronic atrophic (and hypertrophic) arthritis was discussed.⁴³⁰

Factor of Circulatory Disturbance. Sluggish circulation in nail capillaries was found by Dacso in 24 of 32 cases: circulation was normal in eight, slow in 13, decidedly slow in nine and in two entire stasis was seen. Such changes in peripheral circulation, though mild, doubtless influence the production of articular pain and deformity. Using the plethysmograph as a "more accurate method" for measuring circulation in fingers than skin thermometers Ghormley and Silverglade found no consistent vascular reactions or alterations in atrophic arthritis. Circulation was diminished in some cases, increased in others, normal in others. According to Collins¹⁷⁶ some patients with atrophic arthritis under certain conditions present, not an organic obstruction to blood flow, but a reduced flow through smaller vessels. The disorders are of function, not of structure; although blood flow is probably adequate for tissues in a resting state, it is inadequate to permit proper repair of tissues, and is deficient in the presence of physiologic emergencies. Patients with Raynaud's disease react somewhat like those with atrophic arthritis but the two diseases do not produce similar lesions. The vascular disturbances in atrophic arthritis are probably not the cause, but the result of the disease. Apropos thereof Pemberton remarked: "The fact that Raynaud's disease is not accompanied by classical arthritis does not constitute evidence that disturbances in the finer circulation bear no relation to arthritis."

Factor of Altered Metabolism. Attempting to rationalize sulfur therapy in chronic arthritis Wheeldon and Boshier studied the blood and urine in 74 cases of atrophic or hypertrophic arthritis. Results for the two types were not analyzed separately but normal concentrations of glutathione, inorganic sulfates, total sulfur and total sulfates in blood and of urinary sulfates were found. Despite this many patients "improved" on sulfur therapy. The cystine content of nails was high in some of Sullivan's cases of "arthritis," [types not stated], low in others. Since it is low in other diseases the deficiency is not specific or diagnostic. Comroe studied the cystine content of nails in 215 normal persons: the normal variation was greater than previously reported; there was a normal distribution about a median of 9.7 with a quartile dispersion between 8.8 and 10.6. The cystine content of nails was normal in a fair percentage, but low in the majority of 100 cases of atrophic arthritis.

[So far no abnormality of sulfur metabolism in atrophic arthritis has been demonstrated.—Ed.]

Factor of Vitamin Deficiency. The content of vitamin C in serum was subnormal in 75 per cent of the 56 cases of atrophic arthritis of Hall, Darling and Taylor; in 59 per cent it was below 0.5 mg. per 100 ml. (normal 0.8 mg. or higher). Although some patients were taking diets low in vitamin C, none had scurvy. Ten patients tolerated an intake of 100 to 200 mg. without marked excretion in urine; apparently, patients with atrophic arthritis demand much more vitamin C than normal persons. Although patients of Sherwood and Thomson were on diets adequate in vitamin C, their blood was deficient in this vitamin: this was interpreted as indicative of an abnormal vitamin C metabolism rather than a heightened need for it. Similar results were found in cases of hypertrophic arthritis.

[Further studies on vitamin C should be made. Until we have methods for studying the intermediate metabolism of vitamin C the abnormalities observed cannot be interpreted.—Ed.]

Food Allergy. Some patients state that certain foods aggravate their arthritis, but the factor of food allergy in this disease remains unproved. "The matter really appears to be one of fear and distaste, for proof of sensitivity is lacking on skin tests and elimination diets. I have not seen a case" (Monroe).

Intestinal Toxicosis. The supposed rôle of constipation, intestinal toxicosis and colonic irregularities was discussed in the usual vague manner. Some dyspeptic symptoms are the result, not the cause, of the disease.^{275, 325, 415}

Hepatic Dysfunction. There is a growing belief among some workers that the liver plays a rôle in the production of atrophic arthritis. Whether this is a pure metabolic dysfunction or is due to failure of the liver in the work of detoxication is not clear. Chief difficulty is to devise a liver function test delicate or specific enough for use in mild cases.^{182, 187, 539}

Rawls, Weiss and Collins continued their studies of hepatic function in atrophic arthritis. Several tests were used. The azorubin S test revealed hepatic dysfunction (delayed excretion, too rapid excretion, or reduced ability to concentrate the dye) in 60 per cent of 50 cases. Excretion of hippuric acid was abnormal in 62 per cent; it was below normal in 40 per cent, above normal in 22 per cent. [One of us, W. B., has encountered abnormal excretion of hippuric acid only occasionally.—Ed.] The bilirubin excretion test demonstrated delayed excretion in 48 per cent. The galactose tolerance test was not sensitive enough to detect chronic or mild liver damage: it was abnormal in only 14 per cent. In 44 per cent of cases the icterus index was abnormal (above 8). Hypoalbuminemia was present in 68 per cent; an abnormal albumin-globulin ratio, in 76 per cent. No one test should be used as evidence for liver dysfunction. The azorubin S test was considered the best; when it indicated an abnormality, one or more other tests did also.

[It is impossible to interpret these data in terms of etiology because of the doubtful significance of the tests themselves and because the hepatic dysfunction varied in type, not always being a matter of delayed excretion. Since liver dysfunction was not present (by these tests) in all cases, what dysfunction there was must be regarded as perhaps the result, not the cause, of the disease.—Ed.]

Factor of Endocrine Abnormality. Metabolic rates were generally normal, occasionally abnormal (more often below than above normal).

Rates were normal in 60 per cent, subnormal in 35 per cent, above normal in 5 per cent of Potter's 60 cases. Noting that rates were higher among his clinic, than among his private cases Rawls⁶¹⁶ concluded that rates in ambulatory cases are 10 per cent higher than the true basal rates: "therefore all rates of 0 or below should be considered below normal." Thus he considered the great majority of cases to have subnormal rates. [It is difficult for us to accept this view.—Ed.] The rates bore a relationship to the activity of the arthritis; sedimentation rates and nonfilament counts were high in the presence of high metabolic rates, lower in cases of subnormal metabolic rates.

Neurogenic Factors. German workers⁷⁵⁷ considered that in cases of atrophic arthritis toxins from infected foci attack the autonomic ganglia and the anterior horn cells of the spinal cord, producing in effect a type of chronic anterior poliomyelitis with muscular wasting and fibrillation.

Psychogenic Factors. Every practitioner can recall patients whose atrophic arthritis began after severe mental stress—the death of husband or wife, financial loss, etc. Some physicians think that this is coincidental, others do not.^{87, 162, 538, 727}

From a study of 50 cases of atrophic arthritis (and a control series of 25 cases of varicose ulcers) Cobb, Bauer and Whiting concluded that environmental stress (poverty, grief, family worry) bears more than a chance relationship to the onset and exacerbations of atrophic arthritis. "The relative importance of these factors in the etiology of atrophic arthritis can be established only by a much more detailed psychiatric study."

Such a study was attempted by Booth who employed psychiatric tests and the Rorschach method and by Stein-Lewinson who analyzed the handwriting of arthritics before and after development of the disease (cases in which arthritis attacked the writing hand were excluded). Stein-Lewinson studied 31 cases of atrophic and 24 of hypertrophic arthritis but did not analyze the two groups separately. "The arthritic is fundamentally a weak person who overtaxes his inadequate amount of aggressive energy to a considerable degree, distributing it in a disproportionate manner." Certain characteristics are present in his pre-illness handwriting and persist through the disease: they indicate an inadequate vitality which is overstrained by the desire of the patient to hide his weakness. Features which appear after the onset of his disease indicate a breakdown of will power, masochistic sensuousness, hypocrisy, irritability and lessened adaptability. Booth analyzed 45 cases of "chronic arthritis" [types not stated, presumably the same 25 cases of atrophic and 18 of hypertrophic arthritis noted before⁵ plus two new cases.—Ed.] The arthritic's basic characteristics include a predominant instinctual urge to act, susceptibility to influence by environment, a strong consciousness of the laws of behavior of the original environment which leads to sharp restrictions of the active impulses, and a fear of emotional frustration. This personality attitude makes his adjustment difficult and creates a defensive attitude. In summary there was "a remarkably consistent picture of a certain typical dynamic constellation which could be found in all arthritic patients, notwithstanding great psycho-somatic differences in many other respects."

[Neither Booth nor Stein-Lewinson made any attempt to separate the cases of atrophic from those of hypertrophic arthritis. When one considers that the former cases represent a much younger age group, doubtless with greater financial worries and crippling, a group whose lives are "ruined" in their prime and that the latter patients are older, have probably lived full, often successful lives and are only moderately disabled physically and financially, it is difficult to see how any combined analysis of the groups could be other than most general and probably erroneous. It probably represents a psychologic study of so many "sick people," not so many "arthritics." No control cases were studied.—Ed.]

In view of these studies the observation of Gregg that psychotics are relatively immune to arthritis seems strange at first. In Massachusetts one out of every 36 persons in the general population had chronic rheumatism (Bigelow and Lombard, 1933), whereas only one out of 610 psychotics had arthritis. Thus arthritis is 17 times less frequent among psychotics than among others. In 3000 necropsies in psychotic cases "no frank arthritic joints" were found. The "largest arthritis clinic in Boston" has only transferred one of 5766 arthritic patients to the Boston Psychopathic Hospital.

Without extolling the advantages of becoming psychotic, Gregg explained thus: Man is endowed with reactions that enable him to escape from or fight off noxious forces (by increasing his blood pressure, pulse, blood sugar, alertness, etc.). These reactions are beneficial when they occupy the usual stimulus-reaction span of time. But if this stimulus-reaction span of time is unduly prolonged, the result is injurious. Man through his memory and imagination has lengthened the period during which the muscles are tense, the blood pressure raised, etc. These "normal reactions," if unduly prolonged, may produce an increased ischemia of muscles furthering infection and resulting in such conditions as hypertension, angina, gastric ulcer, spastic colitis and arthritis. In childhood and among the feeble-minded or psychotics, imagination and memory have not yet developed, do not develop fully or retrograde. Therefore certain diseases closely related to emotional stress are statistically rare. Thus among psychotic patients without a prolonged stimulus-reaction span, because of impaired imagination and memory, there is little prolonged muscle tension or drag on the joints, little setting of the stage for prolonged ischemia, malnutrition, or infection of joints, and therefore chronic arthritis is rare.

Conclusions on Etiology. Unfortunately this can be very simply stated: nobody knows the cause of the disease.

RELATIONSHIP BETWEEN ATROPHIC ARTHRITIS AND OTHER DISEASES

Rheumatic Fever. English and American physicians are more likely to regard atrophic arthritis and rheumatic fever as separate entities than are Germans and Scandinavians, many of whom think that the two diseases have a common etiology and that atrophic arthritis often results from rheumatic fever.⁷⁵⁷ Regarding both as manifestations of allergy Levinthal and Pagel considered them closely related. But after comparing the connective tissue reactions of the two diseases Collins¹⁷⁷ noted enough differences to state, "If experienced clinicians are prepared to dissociate [the two diseases] the pathologist is not yet in a position to dispute them."

TREATMENT OF ATROPHIC ARTHRITIS

General Remarks. According to their attitude on the treatment of this disease physicians can be classified as (1) the pessimists or nihilists, (2) the optimists and wishful thinkers, and (3) the realists. The pessimists regard all current treatment as essentially useless or merely mildly palliative; on behalf of a patient they may make one therapeutic gesture (usually tonsillectomy, or salicylates probably given intravenously) and when that fails, they say to themselves, "What's the use?" and pack the patient off to a spa or a "rubber." The optimists or wishful thinkers are often, for a time at least, highly successful with their patients. Their radiant optimism is

infectious and serves as potent psychotherapy, but they too often oversell themselves to their patients who expect more than the physician can deliver. These optimists also are in danger of overselling themselves on some remedy and thus becoming faddists. The realist knows full well how inadequate current methods are, how far they are from a truly satisfactory and specific or relatively specific method of treatment, but he also realizes that, while zealously hunting for new tools, he must for the sake of today's patients use today's remedies as vigorously as possible, since thereby he can do much to relieve pain and to prevent or control deformities.

Some recent generalizations on treatment included the following: "Probably no part of medicine is more impotent than that which deals with arthritis," wrote Creer. "Our orthopedic clinics are littered (I can think of no better word) with such cases." The arthritic patient is, "generally speaking, badly treated in the long run, either because the average physician considers the condition unworthy of exhaustive treatment in the beginning or considers it hopeless when well developed" (Wheeldon). "The enthusiastic neophyte tries first, the panaceas described in the best medical journals, next those noted in ordinary medical journals and then quietly sanctions the use of the miraculous cures found in any daily newspaper" (Weinstein). Although no specific remedy is yet available the intelligent application of the best of current methods is productive of worth-while results and patients should not rely on "nature" to stop the disease. "Some patients believe that arthritic pains, like the wicked will flee when no man pursueth but we can assure you that they make better time when the doctor takes after them" (Wyatt and Thompson).

One physician⁸¹⁰ was "unhappy because many of those who are qualified to write on arthritis have been somewhat pessimistic in their attitude toward newer remedies with the result that the family physician accepts the fact in his own mind that nothing new is of benefit. . . . A spirit of optimism—even though conservative—should be developed in the family physician." But the physician's optimism must not be such as would give rise to a conversation recently quoted in an editorial²⁴⁸: "Doctor: 'Well, you've had 3 months' treatment. How are you?' Patient: 'About the same, Doctor.' Doctor: 'But surely you feel a little better after all the trouble we've taken?' Patient: 'Well, Doctor, I'm sure I'm very grateful. Perhaps I do feel a *little* better.' Doctor: 'That's splendid! I felt sure you would.' (Writes on record, 'Improved.')"

"Between a strong therapeutic nihilism on the one hand and wishful thinking on the other, there is a middle ground in the case of arthritics, within which many experienced students and clinicians find cause for great optimism," according to Pemberton. Studies on the effects of jaundice and pregnancy show that the pathologic physiology of atrophic arthritis is more rapidly reversible than was previously supposed. The physician treating arthritis has "already available many, sometimes all, of the varied mechanisms necessary to a true reversal of the disease." But he takes his thera-

peutic cue from those studying the disease and "unless a reasonably wide-angled, and above all, coördinated program be presented to him, he cannot be blamed if he turns from academic negativism to the samples sent him by the drug house." ⁵⁹²

Physicians now realize that until more is known about the natural course of the disease, it is impossible to forecast the particular course which a given case will follow, and equally impossible to evaluate any given treatment (Duthie). The truism "Experience is fallacious, judgment difficult" is especially applicable to a study of the results of treatment in atrophic arthritis. In this disease, the natural course of which has never been adequately mapped out, its chronicity, its irregular tendency to spontaneous remissions, the ineffectiveness of therapy in the more relentless cases, all contribute to the problem of evaluating therapy. The skeptic properly discredits many apparently good results with the assertion "it might have happened anyway." Only when therapeutic results follow some definite uniform pattern which does not occur consistently among any large number of untreated patients can this argument be refuted (Anderson, Lamb, Barritt and Nerb). The Council on Pharmacy and Chemistry ²⁰⁸ suggests that physicians, trying to evaluate remedies for arthritis, use the methods employed by the Council in assessing the worth [or rather, the worthlessness.—Ed.] of sulfur. Before accepting a remedy as valuable "satisfactory evidence must be produced that sufficient controls have been employed and that follow-up periods of sufficient length to rule out spontaneous remissions have been observed. Further, the types of cases in which the preparation may be used with fair expectation of benefit must be determined, and their chief contraindications, optimal dosage and best form and route for use must be defined."

Management of Foci. The year's comments on focal removal produced no new or different ideas on the subject, merely a different set of authors. Since the infectious theory remains unproved, since the removal of an infected focus is rarely the sole form of therapy and is only occasionally followed by prompt improvement, the whole matter remains controversial. A patient with atrophic arthritis and infected foci is in a "less fortunate position" than one with arthritis alone; hence genuine foci of sepsis should be removed.³¹⁰ The medical profession is generally, if unenthusiastically, agreed on this.²⁶³ But there is disagreement as to the optimal time for their removal: according to some, selection of this time requires considerable nicety of judgment. One view is that "the patient must first be rested and built up"²⁶³; another is that delay is generally unnecessary (except in the presence of acute tonsillitis) and the results of prompt removal are "better than if one temporizes with an ineffective program of building up resistance first."⁵⁴²

[Five of us favor the removal of infected foci without delay unless the patient is seriously ill; two of us postpone removal until after a preliminary "build-up." None of us advocates removal of foci as a specific remedy but only as a measure that may improve the patient's general health.—Ed.]

Articular exacerbations which occasionally occur after a focus is removed are "unfortunate" but generally transient and unimportant.^{263, 542}

[We rarely see more than an occasional transient, unimportant flareup.—Ed.]

The removal of infected teeth was approved.²⁶³ Some urged the removal of pulpless teeth,^{263, 631, 755} others did not.⁵⁴² Removal of roots not obviously (i.e., roentgenographically) infected was not approved.¹⁸⁵ Cogan considered the treatment of gingivitis more important than that of infected teeth. But cures following dental extraction are the exception, not the rule. A small percentage of the patients of Vaizey and Clark-Kennedy "appeared to have had a beneficial effect" after alveolectomy for rheumatism, but of 126 patients who had had all their teeth out for purely dental reasons, nineteen later had rheumatism. Fantus urged that tonsils be removed "regardless of their appearance." [Some of us do not agree.—Ed.] Monroe approved this practice for patients under 30 years of age, but urged more discretion in older persons. Hamblen-Thomas believed that the conservative, and if necessary the operative, treatment of sinusitis improved or even "cured" many arthritic patients; but "from bitter experience" Shackle left antrums alone unless they definitely retained pus. Results in the 12 cases of Williams and Slocumb in which sinuses were operated on were not very impressive: six of the patients noted relief, but four of these also had their tonsils removed. Although lateral sinus thrombosis complicating ear infection usually produces acute pyemic arthritis, Asherson considered it a possible cause of chronic arthritis also.

Vaccines, Antigens, Filtrates. Crowe and his colleagues continue to be enthusiastic advocates of vaccine therapy.

Crowe again described his general plan of vaccine therapy^{205, 206, 207} and reported results. Of 212 patients with atrophic arthritis 5 per cent became symptom free, 35 per cent were much improved, 41 per cent were improved, 19 per cent were unimproved. Of 107 patients with "active infective arthritis" 12 per cent became symptom free, 31 per cent were much improved, 38 per cent were improved and 19 per cent were unimproved.

Crowe's vaccine was used by Bunting and by Voss. Of Bunting's 60 patients with rheumatism (type unstated) 13 were cured, 14 much improved, 25 improved, and eight unimproved. Results required "months, not weeks" of treatment. Of Voss' 86 patients 16 were "cured or very much improved," 36 were improved, 34 were unimproved. Weinstein's results with Crowe's vaccine were "disappointing" (no details).

[We cannot share Crowe's enthusiasm for his or for any other vaccine.—Ed.]

Anderson and his colleagues²¹ treated 170 patients with autogenous streptococcal filtrates based on tests of skin and joint sensitivity thereto. The less marked the skin or joint sensitivity the better the results: 23 per cent became symptom free, 5 per cent almost symptom free, 30 per cent markedly improved, 28 per cent slightly improved, 14 per cent unimproved. Reeves enthused about his results from streptococcal antigens selected on the basis of skin sensitivity: when treatment was begun within the first eight weeks of symptoms, "This treatment has not failed in any case." [This is difficult to believe. No details were given.—Ed.] Weiner gave pooled arthrotropic streptococci intravenously in 31 cases. Improvement was marked in none, moderate in seven, transient in 13, absent in 11. Vaccine made from a nonpathogenic air-borne bacillus was used in control cases. When given intravenously in 12 cases (with mild fever reactions) improvement was marked in none, moderate in four, transient in seven, absent in one; when given subcutaneously (without reactions) in 20 cases, improvement was marked in none, moderate in four, transient in seven, absent in nine. Weiner concluded that the streptococcal vaccine was nonspecific and that results are

better when febrile reactions are induced. This was also the opinion of Howitt whose results with vaccine were "unimpressive" (no details).

Reductions in the leukopenic index during vaccine therapy were regarded by Hicks and Wyatt as indices of the amount of desensitization accomplished. Burbank still considered vaccine therapy the best single form of treatment (no details), but Shackle considered vaccine "useless." According to Armstrong there is no standard dose or plan of increasing doses: individual dosage is the sine qua non of vaccine therapy.

Results with vaccines have disappointed most European physicians, who consider them nonspecific and relatively ineffective except as a form of psychotherapy. Having observed their use in many American and European clinics, Tegner concluded, "In the present state of our knowledge of the etiology of rheumatism in general, and of rheumatoid arthritis in particular, the use of vaccines cannot be either endorsed or rejected."

Foreign Proteins. Results therewith were no better and no worse than those with "specific" vaccine, and inferior to chrysotherapy.⁴¹⁰

Autohemotherapy. Ishmael reported that autohemotherapy (10 to 20 c.c. blood) "reinforced" with artificial fever (101.5° F. for one hour, using inductothermy for adults and typhoid vaccine reactions for children) provoked "complete remissions" in all of seven cases of juvenile Still's disease. Results in atrophic arthritis of adults were less notable; among 10 cases, a complete remission resulted once, improvement in four; no improvement in five. Combined therapy was superior to either alone.

Chaulmoogra Oil. Unusual results, at times "truly astonishing," were reported by Stanley. Of 23 cases of atrophic arthritis thus treated results were "100 per cent complete relief" in almost 40 per cent (nine cases), marked (80 to 95 per cent) relief in 26 per cent (six cases), moderate (50 to 75 per cent) relief in 17 per cent (four cases), less marked in the rest (four cases). Patients cured received from one to 45 injections (each 1 to 5 c.c.) intramuscularly. Reactions lasting 24 hours were often produced (fever, headache, malaise, sometimes severe urticaria). Results were less notable in cases of mixed or of hypertrophic arthritis. "Sterile abscesses" occurred in 8 per cent of the cases.

[In view of the experiences of others it is difficult to accept this evaluation. No wonder reprints of this report were circularized (with the title changed) to extol the virtues of a commercial preparation of chaulmoogra oil. The originator of this method of treatment has never made a second report on it.—Ed.]

Bee Venom. Various types of acute and chronic arthritis were treated with bee venom by Ainlay. Of 37 patients 12 had atrophic arthritis. Results which were not analyzed separately follow: 16 were "cured," 16 relieved of pain and the swelling reduced, four improved, one was unaffected. "Thirty-one of our cases have not had any venom for over two months and are still relieved. . . . The one complete failure turned out to be a parathyroid disturbance with muscle spasm and bony deformity." [This report is unimpressive for various reasons, chiefly the unclear method of tabulating results and the short (two month) follow-up. One of the discussors of this paper asked, "Is this an advance in the treatment of rheumatic disease, or is it just another treatment?" Our answer would be the latter.—Ed.] Others²⁵⁵ vaguely approved such therapy but Mackenna, an advocate of bee venom therapy of fibrositis, considered it valueless in atrophic arthritis and had "long abandoned it."

Diets. No really new data appeared but a few comments are reportable. The use of a diet deficient in calories for a few days may induce striking changes in some cases of atrophic arthritis, but in more cases not only inconvenience but definite harm has resulted.³² There is no scientific

distinction between "red" and "white" meat.³² Of 11 patients given 100 gm. of glucose daily with an "ordinary hospital diet" seven were "definitely worse during the time [unstated] they were taking the glucose, and only one of these eventually showed improvement in the sedimentation rate on leaving" (Yeoman). But Miller and Wilson were "not convinced that the so-called Pemberton diet is beneficial in a large majority of cases." Avoidance of "acid items" of diet (tomatoes, oranges, lemons) is harmful, not beneficial, since they are the chief sources of certain essential vitamins. They do not make the body more "acid" or produce an "acid-state." The acids in these foods are only weak organic acids, like citric and malic acids; they are easily oxidized in the body, and their basic elements appear in blood as alkaline carbonates. Hence these "acid foods" actually serve as available alkali.⁵³⁰

The supposed analgesic effect of a "raw vegetable diet" (50 per cent raw fruit and vegetables plus cereal and milk)⁴ results not from its high vitamin C content (as some have contended⁵) but from its altered salt-potassium ratio, according to Pillman-Williams. The diet's content of vitamins A and C and of potassium is high, of sodium low. Such a diet produces analgesia and loss of weight; effects not obtained from ordinary diets plus vitamin C in massive doses, or from the cooked or uncooked diet with added salt.

[The diet was not considered specific; it was used also in cases of hypertrophic arthritis and of fibrositis. No statistical results were reported.—Ed.]

Vitamins. The current frenzy of many physicians is to find the right antirheumatic vitamin.¹¹⁷ Chronic arthritics do frequently exhibit deficiencies of vitamins in their diets or serums or both. Such deficiencies lessen resistance to infection, and infections apparently lessen utilization of vitamins. Hence diets adequate in vitamins are indicated in arthritis. But vitamin therapy is still in the experimental stage and is not yet a rational treatment. Most physicians^{255, 263, 542} advocated the supplemental use of vitamins in ordinary (small) doses, especially cod liver oil and brewers' yeast, but the value of vitamins in massive doses is unproved.

Vitamin A. Some patients with atrophic arthritis are deficient in this vitamin,^{255, 686} but Monroe considered vitamin A concentrates of no value.

Vitamin B. Diets in the cases of Sherwood and Thomson were rarely deficient in this vitamin, and neuritis was even more rarely seen. The vitamin is useful for anorexia and dyspepsia.⁵⁴²

Vitamin C. Whether their diets have adequate⁶⁸⁶ or inadequate³⁵³ amounts of this vitamin, most arthritics have subnormal amounts in serum. Therefore, Hall, Darling and Taylor gave their hospitalized patients with atrophic arthritis 200 mg. of vitamin C daily for eight months. Although the blood became saturated, no improvement attributable to the vitamin was noted.

Vitamin D. Farley again noted marked relief from the use of massive doses (50,000 to 700,000 U.S.P. units daily) of vitamin D (ertron), but he was almost alone in his enthusiasm. Terhune gave 200,000 U.S.P. units

(drisdol) daily for one to four months, then smaller doses (7,500 to 15,000 units) for at least six months. Most of his patients (numbers not clear) were not improved. In some cases subjective relief was noted but Terhune agreed with Abrams and Bauer⁶ that no objective improvement resulted. No significant toxicity was noted; occasional gastrointestinal intolerances were controlled by brewers' yeast. To 35 patients with "arthritis" (types unstated) Andersen and Theis gave 150,000 to 250,000 U.S.P. (XI) units of viosterol daily for several months; only four were notably improved. Weinstein considered it "of no great value" (no details). Ellman's clinical results (no details) "did not support the theory of Dreyer and Reed." The good reports have been "based on uncritical enthusiasm" and there is no rationale for this treatment (Monroe).

It was agreed that the dangers of toxicity have been overemphasized.^{19, 266, 758} Using viosterol in doses stated above, Andersen and Theis noted no hypercalcemia and no significant or consistent alterations in serum calcium, phosphorus or phosphatase. But such therapy generally decreased the serum phosphatase in the cases of Smith, Klein and Steck, especially in those in which ultimate benefit ensued. In Farley's cases ertron generally caused no significant toxicity or changes in serum calcium. According to him other forms of vitamin D generally elevate the serum calcium, may produce toxicity, but may not give relief. He blamed toxicity on the method of activation of the vitamin. "This vitamin D preparation [ertron] is activated from ergosterol by means of an exclusive method (Whittier process), hence differs from the type of vitamin D used by Abrams and Bauer." Therefore the poor results reported by Abrams and Bauer⁶ "are applicable only insofar as the type of vitamin D they employed is concerned and are possibly not applicable to vitamin D obtained by any other process."

[Farley had no control series to support this statement. Others have used ertron without significant results, and, as noted above, other preparations have been used without significant toxic reactions. Certain preparations, notably ertron, are now being advertised vigorously, one might say, offensively, in view of their glowing claims. This therapy is rather expensive when long continued and it is the considered opinion of most of us that it is not worth the money. However, one of us, W. P. H., believes that such therapy will occasionally produce a notable remission and that further work with vitamin D should be done under adequate control in large clinics.—Ed.]

Vitamin G. Dietary deficiencies in this vitamin were common in the cases of Sherwood and Thomson, but no results of therapy were reported.

Intestinal Therapy. Those (rather few) physicians who consider the "reduction of intestinal toxicity" possible and important approved the following: preparations of belladonna for "colon spasm,"²⁷⁵ paraffin oil, other bulky substances, or hot fomentations for constipation or diverticulosis,²⁷⁵ potassium permanganate enemas,³²⁵ colonic irrigations.^{275, 325, 710, 826} Commenting on the latter Patterson stated, "Certain patients are morbidly interested in bowel contents and in these the psychological effect of a good 'decarbonizing' is the chief factor in improvement. It is useless to argue with this type of patient, since, like the advertisement for Pear's soap: 'he won't be happy till he gets it!'"

[We suggest reasoning, rather than arguing, with such patients. There is no satisfactory evidence that the abnormalities and structural irregularities of the colon, sometimes (but not always) seen in weak, emaciated arthritics, are the cause of the

disease. In cases of undoubted classic forms of intestinal disease (typhoid fever, amebic and bacillary dysentery, ulcerative colitis, Hirschsprung's disease) articular symptoms develop with extreme rarity (incidence 0 to 4 per cent), and physicians with critical judgment have long since abandoned "colonic irrigations for auto-intoxication in arthritis" as not worth the time, trouble and expense.—Ed.]

Miscellaneous Medicines. The rôle of drugs, none of which could be regarded as specific, was discussed with the supposed indications for iodine, quinine, strychnine, calcium, iron, insulin (for anorexia and loss of weight), etc.²⁵⁵ Salicylates, especially aspirin, are the most helpful of all as analgesics, but their use to mask symptoms, which thereby leads to the postponement of adequate treatments until the disease has made serious advances, was strongly condemned (Tegner). When aspirin produces too much sweating, the use of extract of hyoscyamus (0.02 gm. per dose) was recommended.²⁶³ Sell reported a case of salicylate poisoning in an eight year old child with Still's disease; after 190 grains each of sodium salicylate and sodium bicarbonate had been given (within five days), sweating, vomiting, abdominal pain, rapid respirations, slight delirium and acidosis with acetone and diacetic acid in urine developed, but recovery followed appropriate treatment. Because of the acid character of ordinary aspirin and the toxicity it may produce, Green³³⁵ recommended calcium aspirin as less toxic, less productive of "acid indigestion," more soluble, and quicker and longer in action.

For fatigue benzedrine sulfate, 20 mg. after breakfast and also after lunch, was recommended; arsenic was considered²⁵⁵ of value in "improving the general tone" [whatever that is—Ed.].

Endocrines. The use of thyroid extract was advised for patients with low metabolic rates.^{255, 616} Rawls said its results were "frequently good in *inactive cases* [italics are ours.—Ed.] of the Marie-Strümpell type."

[Good for what?—Ed.]

Estrogenic hormones were used by some.^{255, 611, 828} The cases in which Yeoman used hydrotherapy plus progynon (10,000 units twice weekly) were the only group in which there was a consistent drop in sedimentation rates. Radnor reported the case of a woman aged 49 years bedridden after 10 months of "typical polyarticular arthritis" unrelieved by heat and gold. Because she had had flushing since the menopause six years before, he gave estrogenic hormone (50,000 units intramuscularly thrice weekly). Within two months she gained 13 pounds and was able to resume work; after two more months she was free of flushes and joint pain, joints moved freely and swelling was reduced (shown in photographs). No other treatment was used. When three days of menstrual bleeding occurred doses of stilbestrol replaced the injections.

Those Other "Remedies!" Here are some data on remedies investigated by the Council on Pharmacy and Chemistry and by others.

Causalin. This was discussed and condemned previously.^{5, 6} It contains aminopyrine. An arthritic patient took over 100 tablets in four months and died of agranulocytic angina.²¹⁵

Aciform II. This is advertised as containing formic acid, alcohol, iodine, sulfur and terpene to be injected at painful sites in cases of lumbago, acute and chronic infectious or traumatic arthritis, sciatica and neuromuscular pains. Among 78 cases of "arthritis" (types unstated) treated by Mayers and Livingston, "improvement" was "complete" in 33 per cent, marked in 43 per cent, slight in 19 per cent, absent in 5 per cent. [In the section headed "Rationale" the technic of administration and *not* rationale was discussed; data on the latter were notable by their absence.—Ed.] The Council on Pharmacy and Chemistry¹⁰⁶ caustically criticized this preparation as "of unscientific composition marketed under a coined proprietary name with exaggerated and misleading claims of therapeutic value. . . . Formic acid preparations can be dismissed from the armamentarium of pharmaceutical preparations without the slightest chance of depriving the sufferer from these [arthritis and associated] conditions of any possible relief."

Condemned as "fakes" were "Zorbit" and "Vita Minro Health Tablets" for arthritis, rheumatism, etc.,¹²⁰ and "Sal Trag" a remedy of secret composition formerly sold as Nue-Ovo; "there is at least one report of severe inflammation of both eyes, with a residual defect in a woman who had taken Nue-Ovo for arthritis."²⁴⁷

Transfusions. No new data were reported.

Sulfur Preparations. Wheeldon again,^{3, 811} with Bosher, recommended sulfur injections. Ellman considered them of benefit in some cases when febrile reactions were induced. Others⁸⁰⁴ wrote "sulphur therapy rests on an elusive theoretical premise that the sulphur content of hair and nails is low in some arthritics" but it is also low in pellagra, malnutrition and other diseases.^{739, 804} Febrile and toxic reactions, sometimes alarming, were produced by the English and American preparations used by Fletcher.²⁸² Some patients showed "slight improvement" but others were "definitely worsened." After reviewing the literature on the subject (85 references) Comroe damned sulfur therapy with faint praise. Of 30 patients given colloidal sulfur (three brands, given intramuscularly, intravenously or both) only 20 per cent noted both objective and subjective improvement; 30 per cent subjective but no objective improvement, 50 per cent were not benefited. Determinations of the cystine content of nails were of no help in predicting which patients would improve. Of a group of controls given injections of a placebo, 20 per cent noted subjective (but no objective) improvement. His results with sulfur were "no better than and in many instances not as good as those obtained by other means." Hence its routine use was not advised.

[Those still inclined to try sulfur for arthritis should read the devastating blast of Freyberg, Block and Fromer at this therapy.—Ed.]

Gold. Chrysotherapy was approved in seven English reports^{171, 207, 217, 255, 302, 410, 756} with general discussions but no data on new clinical series. The latter were given in three American reports.^{452, 650, 711} Tegner reviewed concisely the European and English methods and results from gold.

Indications and contraindications. These were as in previous reviews. Amenable for such therapy are cases of active atrophic arthritis with elevated sedimentation rates, but not inactive cases. Cases of ankylosing spondylitis were considered less (but still) suitable by some, unsuitable by others. The remedy is not helpful in hypertrophic or the specific arthritides or in fibrositis and is contraindicated for patients with atrophic arthritis who have, or have had, hepatic or renal disease, hemorrhagic diathesis, anemia, ulcerative colitis or chronic skin diseases. (except psoriasis which responds well).

Results. "Cures" or marked improvement has occurred rather consistently in 60 to 70 per cent of English and European cases.^{650, 758} American results have been consistently less striking, either because of greater conservatism in their appraisal, or the tendency to use gold in fewer early and more late, resistant cases, or to use smaller, less toxic doses. Key, Rosenfeld and Tjoflat treated 53 patients with myochrysine. The disease of only 6 per cent was "arrested"; 34 per cent of patients were improved "markedly," 25 per cent moderately, the rest little or not at all. Snyder, Traeger and Kelly gave gold sodium thiosulfate to 50 patients with these results: 2 per cent were "cured"; 10 per cent obtained "good," 36 per cent "fair," 52 per cent "poor" results. Results in 80 cases of Sashin, Spanbock and Kling who used mostly gold thiosulfate, in some cases colloidal gold-aurocein (sulphydryl-gold-naphthyl-trisulpho-carbonium derivative) were: cures apparently none, "very marked improvement" in 44 per cent, "moderate or slight improvement" in 39 per cent, no improvement in 17 per cent. Of these 80 cases 11 were of atrophic spondylitis. Improvement was marked in 45 per cent, moderate in 10 per cent, absent in 45 per cent. Thus the results, like those noted abroad, were inferior in spondylitis to those in cases of involvement of peripheral joints.

Results in early cases were notably better in one series⁷¹¹ but not in another.⁶⁵⁰ The effect of chrysotherapy on sedimentation rates was studied. Snyder, Traeger and Kelly did not always find sedimentation rates a reliable index to clinical improvement. Rates were actually higher after, than before, treatment in 47 per cent of the improved cases, and were lower after treatment in 80 per cent of the unimproved cases. But a notable decrease in sedimentation rates was seen in most of Goldie's 400 cases, and clinical improvement was generally proportional to the decrease. The extent of the reduction was entirely determined by that occurring during the first course. But no relationship existed between the initial rate and the clinical result, and determination of the rates was of *no value* in anticipating toxic reactions or clinical relapses.

Dosage. Different plans used abroad were discussed^{171, 207, 756}; dosage varied notably. According to Tegner, Van Breemen's maximal individual dose was only 20 mg.; maximal total dose for a course only 500 mg.; Secher's initial dose was very large, 500 mg., but massive doses of vitamins reputedly prevented toxic reactions. The usual European and English plan was that of Forestier: individual doses up to 150 or 200 mg., total dose for a course 1.5 to 2 gm., two or more courses being given. Tegner's own scheme was doses of 10, 20, 50 and thereafter 100 mg. until a total of 1 gm. had been given; injections were given four to seven days apart and two courses, six to eight weeks apart. Ellman again⁶ reviewed his two schemes: one of large total doses (2 to 2.5 gm.) given to institutionalized patients with high sedimentation rates; one of small total doses (10, 20, 40, 75, thereafter 100 mg. each dose; total

dosage, 1 or 1.5 gm.), for two or three courses six weeks apart. According to Crowe, Irvine, Coke and Beauchamp^{171, 207} set time schedules for successive and increasing doses are bad; doses should be small, not necessarily increased, and should be repeated sometimes days or weeks apart only when the remission after each dose has ended. Their plan of dosage was not stated clearly but depended on changes in their special differential sedimentation test.

The American plans were these: myochrysine, for adults a first dose of 50, thereafter 100 mg. weekly, until a total of 2 gm. had been given, then a second course in six weeks; for children an initial dose of 12.5 mg., thereafter 25 mg.⁴⁵²; gold thiosulfate, first dose of 25, thereafter 50 mg. once or twice a week until a total of 1 gm. had been given⁶⁵⁰; gold sodium thiosulfate, 5, 10, 15, 35, 50, thereafter 100 mg. until a total of 1 gm. had been given, with two courses six or eight weeks apart.⁷¹¹

Toxic reactions. These were as before: mild to marked erythema, exfoliative dermatitis, stomatitis, colitis, diarrhea, vomiting, transient albuminuria, hepatitis, aplastic anemia, eosinophilia, agranulocytosis, bronchitis, conjunctivitis, chills, fever. Sensitive persons may have these after a few doses, others toward the end of a course, or even later.⁷⁵⁶ Toxic reactions occurred in 63 per cent of the cases of Key et al. (108 reactions in 44 cases; reactions were mostly mild, but four were severe: exfoliative dermatitis in three cases, agranulocytosis in one; no deaths); they appeared in only 15 per cent of the cases of Snyder et al. (no deaths but edema of the glottis necessitated tracheotomy in one case); of the cases of Sashin, Spanbock and Kling local reactions (joint pains) occurred in 25 per cent, other reactions (generally mild, severe in three, fatal in no cases) in 24 per cent.

Prevention of toxic reactions. Weekly tests of blood count, sedimentation rate, urine and weight should be made to note impending toxicity.^{255, 756} Some⁴⁵² advised stopping treatment temporarily if leukopenia, eosinophilia, dry skin or pruritus occur. The prophylactic value of calcium gluconate was asserted by Ellman, denied by others.^{452, 711, 756} In an attempt to prevent toxic reactions high carbohydrate diets, liver extract and vitamin C were used by some⁴⁵² but vitamin C was considered valueless by others⁷¹¹; intradermal injections of test doses and patch tests were of no value in detecting hypersensitive patients.⁴⁵² Coke claimed to be able to select cases properly and to prevent all serious toxic reactions by controlling treatment with repeated differential sedimentation tests.

Significant reductions in platelets may denote toxicity with danger of hemorrhage, according to Gasking; hence he urged platelet counts between each dose. The average normal platelet count for males is 351,000 (238,000 to 471,000), for females 398,000 (238,000 to 551,000). There is a normal average variation of 20 per cent. Counts in 20 cases of atrophic arthritis were normal (average total was 380,000; average transient variability, i.e., reduction, 18 per cent). Within three or four days of the first dose of gold the platelet count always decreased notably (average fall 35 to 50 per cent during a course). In some cases counts became stabilized or even increased to normal or above normal (accommodation reaction) but in other cases they continued to decrease. Hemorrhage can occur without thrombocytopenia, but is very likely to occur if platelet counts approach 40,000. Gasking cited a case of Forestier in which fatal cerebral hemorrhage occurred when platelet counts fell to about 30,000. Gasking recommended that small doses of gold be used and given not oftener than every seven days to give the platelets a chance to recover between doses. Treatment of patients whose initial count is 250,000 or less must be cautious; otherwise counts may fall to dangerous levels. The daily use of four oranges did not prevent the reduction of platelets, but the use of vitamin C ("cantan") apparently lessened the reduction by an average of 14 per cent.

Treatment of toxic reactions. Irritations of skin or mucosa "improved rapidly"

from the daily use of 150 to 300 mg. of nicotinic acid. Calamine lotion or colloid baths were used for pruritus, sodium thiosulfate for exfoliative dermatitis, pent-nucleotide for agranulocytosis.⁴⁵²

Mode of action. The bactericidal effect of gold is supposedly negligible.⁴⁶³ Although most gold preparations contain sulfur the amount of the latter is too small to produce results.⁷¹¹ It is the gold which is effective; preparations of gold without sulfur are effective although sulfur may be an adjuvant.¹⁷¹ The mode of gold's action is not known: it may produce mild but prolonged shock therapy, stimulating reactions to toxins.⁷⁵⁶ It may be a "catalytic stimulator" of the reticuloendothelial system or of the general defense mechanism. In normal animals gold is deposited in the cells of the parenchyma of many organs (especially liver, spleen, kidneys and bone marrow), but in animals with chronic infections it is deposited almost entirely in the cells of the defensive reticulo-endothelial system.^{171, 463} Synovial membranes contain numerous reticulo-endothelial cells; such cells in normal animals contain little gold, but in infected animals and in cases of synovial effusion with atrophic arthritis they contain much gold, according to Kling and his associates. Overdosage may poison the very system one is trying to stimulate; hence dosage should be planned to "maintain the minimal catalytic quantity necessary and that will need replacement as the physiologic elimination of gold occurs" (Coke).

Conclusions on the value of chrysotherapy. It is not a cure-all nor should it be adopted as a general measure, according to Tegner. Because of its toxicity it may not be here to stay, but when properly handled, it is a valuable, simple method of treatment available to ambulatory patients; it will often stop or notably affect the disease, not in six years but in six months.⁷⁵⁶ Davidson was unwilling to accept unreservedly current claims for chrysotherapy. It should not be used to the exclusion of orthodox measures.^{217, 302} It is not a safe procedure, but it is worth the risk.⁴⁵² According to Goldie, every patient should be given the opportunity of benefiting from this treatment at the earliest stages. Sashin, Spanbock, and Kling considered it superior to any other present method, but still not the ideal remedy; it will not always stop the disease in early cases. Snyder, Traeger and Kelly were less optimistic: their results were not as good as those reported abroad: it is "too dangerous for general use," and only suitable for patients unrelieved by older remedies.

Vasodilators: Histamine, Choline. Of the 78 patients to whom Kiel gave acetyl-beta-methylcholine chloride (mecholy) by iontophoresis 55 per cent were "completely relieved," 33 per cent partially relieved, 12 per cent not relieved.

[These statistics do not jibe with Kiel's more modest conclusion that "end results in the rheumatoid group are encouraging." There is no treatment of any sort which has consistently "completely relieved" anywhere near 55 per cent of such patients. We suspect that the writer was in a more properly critical frame of mind when he wrote his conclusion than when he made his table.—Ed.]

Similar treatment was given to 35 arthritics (types unstated) by Boyd, Osborn and Markson. Increased mobility and decreased stiffness and pain were sometimes noted. Ellman vaguely approved the use of histamine, thio-histamine or acetylcholine. Histamine by iontophoresis seemed better

than by inunction.⁴⁶² But histamine therapy was "disappointing" to Weinstein.

[These remedies have fewer advocates each year. Current reports were unimpressive.—Ed.]

Sulfanilamide. Large doses for 8 to 27 days failed to produce any effect in 10 cases of Coggeshall and Bauer but presumably improved three cases of Traut and Logan.

Bile Salts. "The majority of arthritics have some liver dysfunction and mild stimulation of the liver with bile salts is advantageous" wrote Burbank. Collins¹⁸² regarded as "satisfactory" her results with bile drainage and injections of decholin (details meager).

[One of us, P. S. H., has recently³⁷⁷ reviewed the generally poor results of others from decholin; its use in his own cases was ineffective.—Ed.]

Rest and Movement. Rest is "the most useful single basic factor in treatment," but it is not a single entity; it is "a mosaic of countless components, some of which may do harm." The "doctrine of rest" does not conflict with the need for nontraumatizing motion of joints at the proper time and in proper amounts.^{592, 781} An ingenious water bed to prevent bedsores and hypostatic pneumonia of bedridden patients, was described.²⁶¹

Physical Therapy. Current articles on the use of various types of physical therapy in arthritis contained little that was new. Students of rheumatism should read Tegner's description and appraisal of methods used in various American, English and European clinics and spas. The importance of physical therapy was everywhere recognized but there were "emphatic" differences of opinion as to the most suitable form for different conditions. Physicians must not buy one machine and use it in all cases; one must choose that type of physical therapy which will give the most relief to the individual patient.⁴⁶⁸ Every therapist should have a "museum room where discarded apparatus in which we once had faith may be placed and catalogued. This would forever furnish a lesson in humility" (Heyman³⁰⁴).

Some general articles on the latest developments in physical therapy appeared.^{203, 470, 471, 502, 532} The case for infra-red irradiation was presented,⁷⁷⁶ but it has recently been shown that even the most penetrating infra-red rays are largely absorbed by the skin.⁴⁷¹ The advantages and contraindications of short wave as contrasted to long wave "conventional" diathermy were debated.^{113, 243, 375, 469} There is no great difference between the two forms, but "short wave diathermy" apparently produces deeper, more uniform heating and is more readily applied.^{193, 195, 473} Fangotherapy is helpful, but inadequate as a sole means of treatment.⁷⁸⁷

Further data on the optimal method of using contrast baths were reported by Collins. Ernst and Woodmansey. These were summarized in last year's Review. In England best reactions were not obtained with the usual one minute hot, one minute cold, one minute hot technic, but with a cycle of eight minutes hot, three minutes cold, or six minutes hot, two minutes

cold. In America (where patients tolerate cold less well than in England) the best technic was five or six minutes in hot water (about 113° F. or 45° C.) and not over two minutes in cold water (about 45° F. or 7.2° C.) alternating back and forth for 30 to 40 minutes, beginning and ending in the hot water.^{470, 471}

The urgent necessity of supplementing professional physical therapy with home treatments was again stressed. "A thirty or forty minute baking or a short wave treatment three times a week will cause very little or no increase of the circulation of fingers, but if this is supplemented by home treatment with hot packs, heating lamps or other measures, much more adequate treatment is rendered."³⁰⁸ Coulter stated that physical therapy once daily is insufficient; it should be applied at short intervals during the day. Simple methods for home treatment were outlined.^{194, 470}

The effects and technic of massage⁵⁴ and also the advantages of various types of hydrotherapy^{244, 470, 590, 593} were reviewed. Hydrotherapy is not indicated in cases of febrile atrophic arthritis.⁵⁹⁰ To ascertain the proper type of hydrotherapy for a given patient the capacity of his skin to perspire must be studied. When in doubt the milder forms of hydrotherapy should be selected until the evidences of free lymphatic circulation and prompt skin reaction warrant the use of stronger forms. "Bath crises" ("getting worse before getting better") can thus be avoided.⁵⁹³ The special advantages of spa therapy were presented.^{38, 116, 393}

Undergraduate education in physical therapy is too meager; the average in 66 medical schools was only 10 hours in contrast to the 30 hours considered the requisite minimum by the Council on Physical Therapy.^{212, 656} The acceptable schools for physical therapy technicians and their essentials were listed.^{401, 402, 403}

Climate. A trip to some "salubrious resort" is beyond the means of most arthritics; were the patient to go there he should stay at least six months or longer; therefore it is fortunate that "a good climate is only a pleasant luxury in the treatment of arthritis" and that "most patients can recover in their native atmosphere, if they have the determination and proper care" (Monroe). Having seen the results of treatment in many diverse climates, Tegner agreed with the foregoing. Arthritic patients (except those with traumatic arthritis) "almost invariably do badly" during sea voyages; acute exacerbations can occur as a result of the constantly varying atmospheric humidity; it is not equable, changing daily, sometimes even hourly (Elder). But changes in humidity and temperature are less important than changes in atmospheric electricity; symptoms increase in the presence of positive charges, decrease with negative charge. Thus the effect of storms varies because the electrical state of the atmosphere is quite as often negative before a storm as after, and may change rapidly according to Monroe.

[No data were given to support these statements.—Ed.]

Occupational Therapy. The value of this therapy combined with physical and other procedures is being recognized more widely. It provides physical and psychologic effects of real importance.^{117, 608, 619} Two English visitors were "greatly impressed" by results of such therapy and by its

wide use in America.^{238, 757} Approved American schools of occupational therapy were listed.⁴⁰¹

Roentgen and Radium Therapy. Scott again strongly recommended local and widefield roentgen therapy. In atrophic arthritis local irradiation was used for palliative purposes, widefield irradiation for its constitutional effects. After local irradiation "possibly 20 per cent do well [but] the number of unsatisfactory results is disconcerting." From widefield irradiation "results are best in the acute rather than in the chronic stages. The effect is frequently delayed 2 or 3 months." Technic was described. [It is difficult to believe that any result "delayed" as long as two or three months is due to roentgen therapy.—Ed.] Eidenow's appraisal was pessimistic: atrophic arthritis is only benefited if treated early; small doses of the medium wavelength gamma rays were preferred to larger doses of hard roentgen-rays of short wavelength. Tegner noted that radiologists were more enthusiastic about roentgen therapy than were their clinical colleagues. Radon was considered of no value.³⁸⁸

Fever Therapy. No enthusiasm for this treatment was recorded. Neymann recommended fever sessions (104° F. for eight hours) in early or more acute cases but gave no results. A few fever sessions were considered useful in enhancing articular circulation prior to orthopedic operations.⁴²⁵ Ferderber recommended a course of fever therapy each spring and fall, but it was difficult to evaluate his results as he had a separate column each for "chronic atrophic," for "rheumatoid," for "acute infectious (non-gonorrheal)" and "chronic infectious (non-gonorrheal) arthritis." Fever therapy reputedly "reinforced" the effects of autohemotherapy in Ishmael's cases. Bromberg's results were "discouraging": only four of 12 patients were improved. Other results were as follows: in one group of 71 patients 11 per cent were "relieved," 69 per cent were "improved," 20 per cent were not²¹⁹; in another group of 10 cases improvement was notable in only five.³⁴⁷ Weinstein considered it "of little value." Elkins and Krusen^{253, 470} did not advise the use of long fever sessions (only 20 per cent of patients thus treated were notably improved), but favored short (30 minute) sessions of fever (101 to 102° F.) every day or so during acute exacerbations, either in a Hubbard tank or fever machine (technic given).

Sympathectomy. This procedure can relieve pain and "improve circulation" but cannot of itself stop the disease.⁵⁸⁵ Selig performed this operation in one case some years ago; death occurred two days after operation.

Nonsurgical Orthopedic Methods. Usual methods to prevent deformities and relieve muscle spasms were discussed.^{139, 278, 340, 408, 679, 781}

In the presence of active inflammation over-exercise produces muscle spasms which may cause deformities; to prevent this rest should be provided by applying light removable splints early before deformities occur.^{403, 598} But Hilton's dictum of "rest for pain" must not be overdone, or ankylosis may result via the "plastic lymph" which pours out from inflamed synovia.^{278, 808} The characteristic deformities and optimal positions for joints were described.^{278, 408} Practitioners should be more familiar with the indications for and technic of these nonsurgical orthopedic procedures; many of them do not require the services of orthopedists but can be done by practitioners and internists in the patient's own home.^{278, 598} The uses of celluloid beds, leather-strip knee braces, leather-cork corsets, cock-up splints for wrists, caliper

splints for weak legs^{284, 408, 480, 598} and also special measures for the care of arthritic feet were discussed. The last consist of rest and strapping, proper shoes, pads and bars, foot baths^{56, 476} and a special foot rest for bedridden patients²⁹⁶ which replaces the ordinary cradle and prevents weakening of feet which may lead to flattening of arches or "foot drop."

Indications and technic for manipulation without anesthesia were described. "The secret of manipulation without anesthesia is the quick short thrust" (Beauchamp). Underwater manipulation is an excellent follow-up to manipulations done with anesthesia.⁸⁰⁸

Surgical Orthopedic Measures: 1. Lactic Acid Injections and Miscellaneous Procedures. Waugh again^{6, 799, 800} described the technic of this procedure which aims to stimulate natural local tissue reactions and evoke processes of repair in traumatized or infected joints. The solution is "prepared by combining lactic acid 0.2 per cent N/5 with procaine (novocaine) 2 per cent and 0.5 per cent NaCl" to make a sterile, approximately isotonic anesthetic with a pH of 5.6 to 5.8. Supplementing intra-articular injections were certain orthopedic measures (manipulation and splinting), but control joints for which injections were not used were but little improved. Fifty patients with inactive atrophic arthritis so treated obtained "at least 50 per cent recovery of function." In no case was inflammation clinically active.

Again discussed were the indications for and technic of arthrotomy and lavage with Dakin's solution,²⁷⁸ arthrodesis,^{278, 408, 702, 679} osteotomy (not very suitable in atrophic arthritis as it demands too long fixation)^{278, 673} pseudarthrosis,^{340, 673} excision of joints,^{139, 278} arthroplasty^{14, 139, 278, 408, 673} and special measures for deformed feet.⁴⁷⁶ For an arthroplasty to be successful there must be sufficient healthy muscle to move the newly formed joint; since these are often absent in arthritics failure often results and joints may restiffen.^{278, 673}

Synovectomy was done by some in chronic quiescent cases,^{673, 794} by others^{278, 585, 745} in active cases "predominantly synovial," without much bone change or capsular fibrosis. Capsulotomy was recommended for flexed knees; it may not increase the range of motion but will transfer that range of motion to a more useful part of the arc.^{278, 673}

2. Manipulation under Anesthesia. The indications and technic of manipulation were reviewed.^{57, 58, 234, 278, 476, 532, 533, 594, 808} Evipan or pentothal sodium were the anesthetics of choice. Results were good in knees, feet and ankles, poor in elbows, wrists, fingers and hips. Manipulation of shoulders is beneficial when restriction of motion involves the lower 60 degrees of the arc of abduction but not when it involves that from 60 to 120 degrees or all directions ("frozen shoulder").

Some advocated manipulation even in mildly active cases.^{57, 234} It is often delayed too long; when done early for joints only slightly stiffened, it may save weeks of physical therapy by heat, massage, etc. Others approved manipulation only when active inflammation is entirely gone.^{278, 532, 533} It should be approached with great caution and only be done by the skilled. Manipulation of joints which are notably destroyed is futile and dangerous. Most failures are due to overzealousness. Mennell cited the death of an arthritic patient 48 hours after a too vigorous manipulation. His advice was never to rely on an old roentgenogram, for osteoporosis occurs rapidly.

A series of manipulations is superior to one. A wise man does less than he might and does it more than once; a rash man takes a chance and goes out for full range. But he should remember that it is not his knee, the subsequent pain and reaction will not be his, nor will he suffer (save in reputation and possibly remorse) the pangs of disappointment when intense suffering reaps no reward. Mobility and pain are incompatible, hence any painful reaction must be transitory if one is to regain any degree of voluntary movement. If after 24 hours the patient cannot voluntarily move the joint without undue discomfort, through as wide a range as before manipulation, too much was attempted.

3. "*Vitalium Mold-Arthroplasty.*" Arthroplasty has previously consisted in reshaping two joint surfaces and covering them with a lining that tended to prevent ankylosis, but blood clots within the joint after operation too often formed a fibrous tissue scar limiting motion. If the clot was confined to the capsular region and did not involve the interposed lining, less stiffness resulted. With this idea in mind Smith-Petersen (1925) developed the "two-stage mold arthroplasty" whereby an inert mold was inserted, around which nature could do its repair work. Early molds of glass, viscaloid and pyrex, were inadequate; bakelite was better, but vitalium was the best, and a new technic was developed with molds inserted into hips, and held in place by position only. When they were removed 21 to 25 months later, highly developed hyaline cartilage had covered the joint surfaces and the newly formed capsule consisted of dense fibrous tissue with a true synovial lining. Smith-Petersen has done this procedure in 29 cases since June, 1938 but it is too early for end results to be reported. He now thinks that the molds need not be removed.

Aware of Smith-Petersen's "unpublished work" with molds of various kinds, Hopkins and Zuck independently selected vitalium as a superior medium and performed an arthroplasty with such a cup February 11, 1938; the paper was published in July, 1938; at the time of a second report the results were "remarkable." Campbell¹³⁹ devised a vitalium cup for knee joints, but has used it in only four cases and has made no conclusions as yet.

[This work of Smith-Petersen is stimulating and most interesting. The method seems to promise results superior to older ones. We understand that results are best for ankylosed hips in which inflammation has ceased, and inferior (to date) in hips still the site of active atrophic arthritis.—Ed.]

4. *Removal of Patella.* This new procedure is advocated for arthritic knees affected by stiffness, pain and grating from osteophytic outgrowths due to various kinds of arthritis. Howell⁴⁰⁸ reported "great benefit" therefrom in an unstated number of cases. The 11 patients operated on by Berkeiser included four with atrophic, three with hypertrophic, two with gonorrheal and two with traumatic arthritis. Thereafter there were less pain, more motion and a greater ability to maintain extension due to increased strength of the quadriceps. It is "not a specific treatment" for arthritis but a means of removing a mechanical impediment to function resulting from patellar exostosis.

[Results were not analyzed statistically.—Ed.]

Psychotherapy. Booth and Gordon³²⁸ regarded psychotherapy as an important adjunct to other remedies. The patient's recovery and freedom from relapses depend largely on the degree of his emotional stability and on the satisfactoriness of his philosophy of life. "Chase out the 'jitterbug' and other bugs won't find it nearly so easy to thrive."³²⁸ This can be done by altering his feelings of frustration through combined medicinal, physical and psychotherapy.

Prognosis: End Results. A third of Monroe's 267 clinic patients seen over a 10 year period did not return; of those treated for six months or more 40 per cent had "good results," 29 per cent had "fair improvement" and 30 per cent were "unimproved or worse." Those treated longest had the best results. Data on the life course of arthritis were again reported^{2, 3, 563} by Nissen and Spencer: of 102 patients with "rheumatoid arthritis of unknown etiology" three took course A (one attack, practically full recovery), 44 took course B (remissions and relapses through life), 105 took course C (slow progressive crippling until death an average of 19 years later), nine took course D (rapid crippling and early death an average of seven years later).

STILL'S DISEASE

Little on Still's disease appeared. Atkinson published a historical and clinical review. Orthopedic measures for the deformed joints of arthritic children were reviewed.⁶⁷⁹ A case of Still's disease in a girl aged seven years was reported⁴¹⁸ as unusual because amyloidosis, unsuspected during life, was found at necropsy.

[In our experience amyloidosis occurs frequently, rather than rarely, in Still's disease.—Ed.]

EDITORIAL

HUMORAL FACTORS IN THE CONTROL OF HYPERTENSION

THE demonstration by Goldblatt and his associates that injury to renal tissue produced by ischemia may result in sustained hypertension has stimulated a search for some substance to explain this activity. Some of the implications of Goldblatt's work have been discussed editorially in this journal.¹ It has been shown that the pressor response is not dependent upon the nervous system. The endocrine glands apparently play only a subsidiary part. Removal of the damaged kidney, however, abolishes the hypertension if the other kidney is normal. These facts led Goldblatt to suggest that the hypertension was excited by some substance that was formed in the damaged renal tissue.

The presence of pressor substances (renin) in extracts of renal tissue was first reported in 1898 by Tigerstedt and Bergmann.² This finding has since been corroborated by a number of investigators, although attempts to demonstrate an increased quantity of pressor substance in ischemic kidney tissue as compared with normal kidney have not been convincingly successful. The nature of the pressor substance (renin) in normal renal tissue has been studied extensively by Page and his associates.³ On injection into normal animals renin causes a rise of blood pressure, and on perfusion through the rabbit's ear or through isolated organs it causes constriction of the vessels. On slow infusion into animals it causes a constriction of the renal vessels which, according to Corcoran and Page, is particularly marked in the efferent glomerular capillaries, thus resembling the condition which has been described in essential hypertension in man.

If, however, purified renin in Ringer's solution is perfused through a rabbit's ear, no vasoconstriction occurs. Renin requires for its activity some protein-like substance present in normal serum, which has been termed "renin-activator."⁴ Renin is also probably a protein, it is thermolabile and in many other ways resembles an enzyme. Its action is slow in developing, it is affected by temperature, and the quantity of renin required for maximal effect is minute (1 to 30) as compared with that of "activator." The latter is probably the substrate.

The product of their interaction has been termed angiotonin. This has been isolated in relatively pure crystalline form by Page and Helmer⁵ as an

¹ ANN. INT. MED., 1938, xii, 267-268.

² TIGERSTEDT, R., and BERGMANN, P. G.: Niere und Kreislauf, Skand. Arch. Physiol., 1898, viii, 223-271.

³ PAGE, I. H.: On the nature of the pressor action of renin, Jr. Exper. Med., 1939, lxx, 521-542.

⁴ KOHLSTAEDT, K. G., HELMER, O. M., and PAGE, I. H.: Activation of renin by blood colloids, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 214-215.

⁵ PAGE, I. H., and HELMER, O. M.: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator, Jr. Exper. Med., 1940, lxxi, 29-42.

oxalate and a picrate. It is a thermostable fluorescent substance soluble in water and alcohol and gives the color reaction for arginine but not those for the other aminoacids. On further incubation with renin it is gradually destroyed, and it is thought to be an intermediate product of the reaction between renin and renin-activator. A single injection into an animal causes a sharp rise in blood pressure, somewhat more prolonged than that produced by adrenalin, and a continuous infusion will maintain a high pressure for some time. It differs radically from adrenalin in other respects, however. The latter shows relatively little tendency to lose its effects after repeated injections. If, however, repeated injections of renin are administered to an animal, there is a progressive diminution of the responses obtained, and after about six doses the animal becomes refractory—a condition which Page et al. have termed "tachyphylaxis." They have shown that in part this state is owing to exhaustion of activator in the blood. Transfusions of blood from a normal animal, however, and even injections of a mixture of renin and renin-activator which is active in a normal animal, fail largely or completely to elicit a response in such a tachyphylactic animal. Renin added to blood from a tachyphylactic animal will not cause vasoconstriction when perfused through an isolated rabbit's ear. These facts suggest that renin injections stimulate the production or the liberation into the blood of some neutralizing antipressor substance.

There are a number of observations which indicate that the kidney may be the source of such a substance. Thus removal of the healthy kidney from a Goldblatt dog made hypertensive by partial obstruction of one renal artery greatly increases the hypertension. Bilateral nephrectomy (after the lapse of some hours) greatly increases the response to renin or angiotonin, both when injected into the animal and when added to the serum of such an animal and perfused through a rabbit's ear. Massive transfusions of normal blood abolish this hypersensitiveness, possibly by supplying the deficient inhibitor.

The extraction of such an inhibitor from kidney tissue was first reported by Grollman, Williams and Harrison.⁶ They obtained in partially purified state a water soluble nonprotein substance, stable in dilute acid solution. This did not lower blood pressure in a normal animal but did so substantially in rats made hypertensive by partial nephrectomy, in Goldblatt dogs and in a few human cases. It was active by parenteral injection and also when administered by mouth. It reduced the response in normal animals to injections of renin. In animals with grave hypertension the fall in blood pressure might be accompanied by a severe reaction with prostration, anorexia, vomiting and uremia. The blood pressure gradually rose to its previous level a few days after the administration was stopped.

An extract containing a depressor substance probably identical with this

⁶ GROLLMAN, A., WILLIAMS, J. R., and HARRISON, T. R.: The preparation of renal extracts capable of reducing the blood pressure of animals with experimental renal hypertension, *Jr. Biol. Chem.*, 1940, cxxxiv, 115-121.

was independently obtained by Page et al.[†] by means of somewhat different procedures, both from normal kidney tissue and from muscle. It caused a drop in blood pressure when administered to dogs with hypertension produced by a cellophane perinephritis, as well as in hypertensive rats. The relief of associated symptoms in these animals is said to have been marked. In some cases extensive retinal lesions subsided and renal function improved. The effect gradually passed off after treatment was stopped, but it was usually maintained for from 4 to 40 days. Too precipitate lowering of the blood pressure, however, might result in uremia and fatal collapse.

They also report the administration of the extract to six cases of essential (benign) hypertension and to five cases of malignant hypertension in man. The blood pressure was lowered significantly in all, and symptoms were largely relieved. The effect was not maintained after treatment was stopped. Their results are somewhat confused by the fact that some of the extracts used were apparently not potent.

They point out that this substance differs essentially from other known depressants, particularly in the fact that its action is slowly elicited (12 to 48 hours), and that it is maintained for some days.

The significance of these observations is still uncertain and can be established only after much more study. It is not certain that the "hypothetical effect substance" of Goldblatt, presumably liberated from ischemic kidney tissue, is identical with the renin obtained from normal kidneys. Neither is it certain that either renin or the depressor substance is a normal secretory product of the kidney. Either might be simply degradation products of the kidney tissue. The evidence, however, does suggest the possibility that they may be antagonistic hormonal substances secreted by the kidney, and that under normal conditions the relative amounts liberated are so adjusted as to maintain the blood pressure within the usual limits. In the Goldblatt dog there appears to be an excessive formation of a pressor substance. In some other conditions the primary disturbance might be a deficient production of the depressor substance.

As to the therapeutic use of such products in hypertension in man, at best the results so far reported merely warrant further trial in hospitals under rigidly controlled conditions. In a disease as variable in its course as this, such experiments would have to be carried out on a large scale and over a period of several years before any definite conclusions could be drawn. The great importance of the subject, however, amply justifies the effort and expense which will be required to carry out such a study adequately.

P. C.

[†] PAGE, I. H., et al.: Reduction of arterial blood pressure of hypertensive patients and animals with extracts of kidneys, *Jr. Exper. Med.*, 1941, lxxiii, 7-41.

REVIEWS

Fundamentals of Biochemistry. By T. R. PARSONS, B.Sc. (London), M.S. (Cantab.) Sidney Sussex College, Cambridge. Sixth edition. 461 pages; 13 × 19 cm. William Wood and Co., Baltimore. 1939. Price, \$3.00.

This most recent edition of a volume which appeared originally in 1923 includes an entirely new chapter devoted to the sterols, their derivatives, and their function in the body mechanism.

In a book designed to fit the needs of a beginning student of physiology, the author has succeeded in keeping his subject matter intelligible to those who have had a minimum of previous knowledge in pure physics and chemistry. The author, in his foreword, alludes to what is undoubtedly the worst fault of the work—oversimplification of the physiological and chemical processes which govern the intricate mechanical device which is the human body.

Of necessity, a book, covering so broad a field in 424 pages, must be confined to the barest outline. Indeed the author believes that no single work can ever suffice for an intelligent understanding of the subject but must be supplemented by comparison with as many sources as possible. It is only after such pursuit that the student can "realize" his subject and become truly inspired by the combined intellectual attainments of scientists everywhere. Toward that purpose the author has concluded each chapter with comprehensive bibliographies for further investigation.

He opens his book with a discussion on the nature of living matter. This is followed by a résumé of the chemistry of the proteins, their properties and functions, metabolism, and the nitrogenous exchanges of the body as a whole. This section of the book is especially well organized and coördinated. Next in order he considers the fats and their relatives, the phospholipides and their place in human physiology. Following this is the chemistry of the carbohydrates, their metabolism, utilization, and pathology.

The remaining chapters are devoted to enzymes and oxidation catalysts, the vitamins, body pigments, the respiratory gases and gas tensions, and finally the functional importance of body fluids, both colloid and electrolyte.

For a broad, continuous version of the chemistry behind human physiology this volume should prove to be helpful to student and physician alike.

E. J. P.

Chemistry and Medicine. Edited by MAURICE B. VISSCHER, Professor of Physiology at the University of Minnesota. 296 pages; 15.5 × 23.5 cm. University of Minnesota Press, Minneapolis, Minn. 1940. Price, \$4.50.

One of the most recently developed and most rapidly expanding aspects of medical science is that of chemistry. Because of the ever increasing interest in the field the committee which was planning for the celebration of the fiftieth anniversary of the founding of the University of Minnesota Medical School decided to limit the scientific program to the one theme: "Some Trends in Medical Progress with Particular Reference to Chemistry in Medicine." And it was because of the general excellence of the papers delivered before this assembly that this volume was published.

Under the editorship of Dr. Maurice B. Visscher the fourteen papers comprising the program were collected, edited, and published for the benefit of those who heard them delivered and the many others who will find these papers of interest.

Each of the papers delivered by men well known and highly regarded in their

respective fields is worthy of individual analysis, but the writer will confine himself to the general outlines of the topics. The book is divided into four sections, each section of which consists of three or four papers.

The first section is devoted to progress in the application of physical chemistry to medicine. Colloid chemistry and osmotic work in living systems is discussed by Dr. Herbert Freudlich and Dr. Maurice Visscher respectively. Such a discussion is necessarily highly technical but the speakers have assembled tables and charts to simplify and tabulate their subject matter. The final paper of the section is one delivered by Dr. John P. Peters on some reactions by which solutes may be differentially concentrated by the kidney.

The second section is one devoted to recent investigations in metabolism. It consists of reports of the studies made by Lee Irwin Smith in vitamin research and George O. Burr on the necessity of fats in the diet. Dr. Charles H. Best concludes the section with a review of the work being carried on at the University of Toronto with regard to heparin and thrombosis. He concludes his discussion with the results they have had with heparin used in various types of vascular surgery, in transfusions, and in cases of subacute bacterial endocarditis.

The third division of the book deals with immunity and chemotherapy. Dr. Michael Heidelberger recalls that it has been just 50 years since the relationship between pneumonia and the pneumococcus was discovered and how slowly but surely advances are being made in the field of immunology and serology. In his own words "It is apparent that new organic chemical techniques, powerful physico chemical tools, the application of vigorous quantitative micro methods of analytical chemistry, and the theories that have emerged from such methods have advanced our understanding of the chemical bases of immune processes to a considerable degree."

This quotation could be so aptly applied to a great number of fields especially that of the little known animal viruses upon which Robert G. Green spoke and that of the highly publicized and ever growing study of sulfanilamide and its derivatives and their mode of action upon which Dr. Perrin H. Long of Johns Hopkins University spoke.

The final section of the book is confined to the study of the nervous control of the organism and consists of talks by Drs. Irwine MacQuarrie, Herbert S. Gasser, Detlev W. Bronk, and Walter B. Cannon.

The volume is an interesting and valuable addition to any medical library and though the topics discussed are of a technical nature they are concisely and reasonably explained.

E. J. P.

Vitamin Therapy in General Practice. By EDGAR S. GORDON, M.D., M.A., and ELMER L. SEVRINGHAUS, M.D., F.A.C.P.; With a foreword by C. A. ELVEHJEM. 258 pages; 14.5 × 21 cm. The Year Book Publishers, Inc. Chicago, Illinois. 1940. Price, \$2.75.

Here is very readable, concise and up-to-date information for physicians who need guidance to recognize the earlier manifestations of deficiency diseases and to prescribe effectively either with diets or preparations of vitamins. Advance in the nutrition field has been so rapid and the literature has become so voluminous, that few are able to keep abreast. This handbook is written by men who are well prepared for the task, and proper use of the information it contains will contribute importantly to the successful practice of medicine.

R. M. W.

Complete Guide for the Deafened. By A. F. NIEMOELLER, A.B., M.A., B.S.; With a foreword by HAROLD HAYS, M.D., F.A.C.S. 256 pages; 14 × 21 cm. Harvest House, New York. 1940. Price, \$3.00.

It is not always considered wise that patients should know too much regarding their own ailments, but there are certain chronic incurable diseases attended by physical handicaps to which individuals so affected must adjust their lives, that they may be lived to the best advantage. Of such diseases, few, if any, are more common than those of the ear leading to hardness of hearing of greater or less degree. People who are deafened, near or below the average conversational level, are seriously hindered both from a social and occupational standpoint; but they are usually allowed to leave the office of the busy otologist, who has honestly told them there is nothing further he can do, without a word regarding certain adjustments that can be made or rehabilitation which may bring their lives nearer the normal. That they go away to become the victim of every charlatan with a new "cure" is not to be wondered at; that they accept each and every elaborate and expensive treatment with aroused hope is not surprising; and that finally they become introspective and skeptical, avoiding and rejecting all means of amelioration is only human. To meet this condition, Mr. A. F. Niemoeller has written the *Complete Guide for the Deafened*, and it would be a carpentering otologist, indeed, who would hesitate to place this book in the hands of any hard of hearing patient.

The author has particularly stressed the necessity of careful ear examinations and treatments by competent otologists. The authorities he has quoted are among the most outstanding American aurists of recognized scientific and clinical ability. New or experimental treatments are mentioned only if sponsored by recognized investigators, and any controversial factors are freely admitted. Recognition of deafness in children and its prevention is emphasized. The value of hearing-aids both individual and group, with their proper use is well handled. Lip-reading and its limitation is described. As a matter of fact, there are few if any phases of ear diseases, and the deafness resulting therefrom that are not adequately touched upon in the 77 very short chapters into which the author has divided his book.

The style is simple, accurate, and most readable. One might feel that some of the chapter headings are a bit sensational as compared to the conservative contents of the text itself, but this is only mentioned as a constructive criticism of form.

The book is profitable reading for all otologists who wish to keep abreast of the social aspects of deafness. It should be in the library of all Leagues for the Hard of Hearing, and it may be safely recommended to all deafened people, who are anxious to reconstruct their lives to meet their handicap.

J. W. D.

Military Preventive Medicine. By GEORGE C. DUNHAM, M.A., M.D., Dr. P. H., etc.; Lieutenant Colonel, M.C., U.S.A.; Director, Department of Preventive Medicine, Army Medical School. 3rd. edition. 1198 pages; 16 × 23.5 cm. The Book Service, American Public Health Association, 50 West 50th Street, New York, N. Y. Price, \$2.50.

Colonel Dunham presents well the principles of Army epidemiology and sanitation. The many illustrations make the subject matter of the text readily understood. This volume should be invaluable to the many physicians now entering the Army Medical Corps.

W. S. L., JR.

COLLEGE NEWS NOTES

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1941-42, are herewith announced and published:

President-Elect James E. Paullin, Atlanta, Ga.
First Vice President D. Slater Lewis, Montreal, Canada.
Second Vice President Thomas F. Holt, Wichita, Kan.
Third Vice President Samuel E. Munson, Springfield, Ill.

The election of nominees shall be by the members of the College at its Annual Business Meeting, Boston, Mass., April 24, 1941. These nominations do not preclude nominations made from the floor at the Annual Meeting itself. Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,

Reginald Fitz, Boston, Mass.,
Fred M. Smith, Iowa City, Iowa,
Charles F. Tenney, New York City,
Ernest B. Bradley, Lexington, Ky.,
David P. Barr, *Chairman*, St. Louis, Mo.

Committee on Nominations

SPLENDID COURSE IN MILITARY MEDICINE OFFERED MEMBERS OF THE AMERICAN COLLEGE OF PHYSICIANS

Through the collaboration of the Army Medical Corps, the Navy Medical Corps and the United States Public Health Service, an unusual postgraduate course in Military Medicine has been arranged for members of the College who are interested. This course will be given in Washington, D. C., from April 7 to April 19.

Many subjects will be presented by outstanding experts from military, naval and civil life. Although stress will be placed upon the relationship of professional activities to the Preparedness Program and to possible war, the subjects will be of a strictly medical nature. Venereal diseases, tropical medicine and infectious diseases will be considered in great detail, as well as many other subjects that should be of considerable interest to internists and physicians in general. Washington is now overflowing with medical talent, and this has been commandeered for the course. Furthermore, experts from afar are being invited to participate. Members attending this course will have an opportunity to observe at first hand the outstanding medical institutions of the National Capital. Whether they are interested in participation in the Preparedness Program or not, they should receive a great deal of helpful information.

One of the most pleasant times of the year to visit Washington is April. The weather is usually excellent, and the city is beginning to take on its Spring beauty. Although the course will consume the greater part of the time, there will undoubtedly be ample opportunity for sight-seeing.

This course is a new venture for the American College of Physicians, and it is hoped that a sufficient number of Fellows and Associates will sign up for it to make it worth while for the instructors to exert their best efforts.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Tomás Cajigas, Washington, D. C.
 Dr. Gustave William Dishong, Omaha, Nebr.
 Dr. Harrison Fitzgerald Flippin, Philadelphia, Pa.
 Dr. Emmet F. Horine, Louisville, Ky.
 Dr. Ontie Hovenden, McGill, Nev.
 Dr. Alexander B. Leeds, Chickasha, Okla.
 Dr. Jesse M. W. Scott, Schenectady, N. Y.
 Dr. Jacob Segal, New York, N. Y.
 Dr. Thomas H. A. Stites, Cresson, Pa.
 Dr. Warren Thompson, Omaha, Nebr.
 Dr. John Walter Torbett, Sr., Marlin, Tex.
 Dr. Louis A. Van Kleeck, Manhasset, N. Y.
 Dr. I. Ogden Woodruff, New York, N. Y.

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Books

Dr. William S. Hoffman, F.A.C.P., Chicago, Ill.—“Photometric Clinical Chemistry”;
 Dr. Maurice Lewison, F.A.C.P., Chicago, Ill.—“Manual of Physical Diagnosis”;
 Dr. John Walter Torbett, Sr., F.A.C.P., Marlin, Tex.—“Practical Poems for Daily Use”;
 Dr. Paul D. White, F.A.C.P., Boston, Mass.—“Electrocardiography in Practice.”

Reprints

Dr. H. Sheridan Baketel, F.A.C.P., Jersey City, N. J.—1 reprint;
 Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—2 reprints;
 Lt. Col. J. R. Darnall, F.A.C.P., (MC), U. S. Army—2 reprints;
 Dr. Eugene H. Drake, F.A.C.P., Portland, Maine—2 reprints;
 Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—2 reprints;
 Dr. Joseph F. Elward (Associate), Washington, D. C.—1 reprint;
 Dr. Jason Engels Farber (Associate), Buffalo, N. Y.—1 reprint;
 Dr. Lynn T. Hall, F.A.C.P., Omaha, Neb.—1 reprint;
 Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
 Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—1 reprint;
 Dr. Edward Kupka, F.A.C.P., Olive View, Calif.—6 reprints;
 Dr. Perry Scott MacNeal (Associate), Philadelphia, Pa.—1 reprint;
 Dr. Harold R. Merwarth, F.A.C.P., Brooklyn, N. Y.—1 reprint;
 Dr. Curtis T. Prout, F.A.C.P., Arlington Heights, Mass.—1 reprint;
 Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—23 reprints;
 Dr. Martin Van Buren Teem, F.A.C.P., Marietta, Ga.—1 reprint;
 Dr. Harry B. Thomas (Associate), York, Pa.—1 reprint;
 Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif.—1 report.

1941 JOHN PHILLIPS MEMORIAL AWARD

On the recommendation of the Committee on Fellowships and Awards, the Board of Regents of the American College of Physicians, by unanimous resolution, has voted that the John Phillips Memorial Medal for 1941 be awarded to Dr. William Christopher Stadie, Associate Professor of Research Medicine at the University of Pennsylvania, Philadelphia, for his significant contributions to the knowledge of anoxia, cyanosis and the physical chemistry of hemoglobin, and more especially for his recent studies on the subject of fat metabolism in diabetes mellitus.

OKLAHOMA MEMBERS HOLD REGIONAL MEETING

The members of the American College of Physicians in Oklahoma held their annual meeting, February 22, 1941, in Oklahoma City, under the Governorship of Dr. Lea A. Riely, F.A.C.P. There were clinics and round table discussions during the day and a dinner and social meeting in the evening.

In addition to the annual meeting on February 22, the College members in Oklahoma, in conjunction with the Oklahoma Internists Association, each year furnish one day's program at the meeting of the Oklahoma State Medical Association. This group also has a "get together" meeting at the Annual Fall Clinical Conference of the Oklahoma City Clinical Society.

Dr. Everett C. Fox, F.A.C.P., Dallas, Tex., was elected a member of the Board of Directors of the American Academy of Dermatology and Syphilology for a three-year term at the annual session of this society in Chicago, December 8-10, 1940.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., has been chosen as the first recipient of the John Jeffries Award. This award was presented to Dr. Bauer at the Honors Night Dinner of the Institute of the Aeronautical Sciences on January 28, 1941. The John Jeffries Award, which is given for contributions to aviation medicine, was established in honor of the first American to make scientific observations from the air. The Institute will present the John Jeffries Award annually for outstanding contributions to the advancement of aeronautics through medical research.

Dr. Bauer, the recipient for 1940, was the first Medical Director of the Aeronautics Branch of the Department of Commerce. He organized and was the first President of the Aero Medical Association and is now Editor-in-Chief of its official publication, the Journal of Aviation Medicine. He is consultant in aviation medicine and cardiology to the Civil Aeronautics Authority.

Dr. James B. Bullitt, F.A.C.P., Chapel Hill, was elected President of the North Carolina Pathological Society at its recent annual meeting in Charlotte, and Dr. C. C. Carpenter, F.A.C.P., Wake Forest, was reelected Secretary and Treasurer of the Society.

Dr. William Gerry Morgan, M.A.C.P., Washington, D. C., was elected Chairman of the newly formed Washington branch of the American Bureau of Medical Aid for China at a meeting held recently at the Chinese Embassy in Washington.

On March 14, 1941, Dr. Harold J. Harris (Associate), Westport, N. Y., will give a radio address on the subject of "The Relationship of Brucellosis (Undulant Fever) to Tuberculosis" over station WNYC, under the auspices of the New York Tuberculosis and Health Association.

The Executive Board of the American Public Health Association has announced that this Association will hold its 70th Annual Meeting in Atlantic City, N. J., October 14-17, 1941.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Newer Nutrition and Its Application to Clinical Medicine" to the Staff of the Cooper Hospital in Camden, N. J., on December 13, 1940.

Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I., spoke on "Electrocardiography" at the monthly meeting of the Pawtucket Medical Association, December 19, 1940.

On January 8, 1941, Dr. Kenney took part in a symposium on "The Medical Management of Pre-Operative Phases of Biliary Tract Disease" at the combined meeting of the Worcester City Hospital Staff and the Worcester District Medical Society.

Dr. J. Arthur Buchanan, F.A.C.P., Brooklyn, N. Y., has been named Director of Medicine at the Wyckoff Heights Hospital by its Board of Trustees, with authority to reorganize the medical service at that hospital.

The New Jersey Gastro-Enterological Society held a symposium on "Lesions of the Stomach, Duodenum and Jejunum" at the Academy of Medicine, Newark, N. J., February 3, 1941. Dr. Hyman I. Goldstein (Associate), Camden, N. J., presided at this meeting. Among others who participated were: Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.; Dr. Charles L. Brown, F.A.C.P., Philadelphia, Pa.; Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J.; Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.; and Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.

The Third Annual Forum on Allergy was held in Indianapolis, Ind., January 11-12, 1941. Dr. Bela Schick, New York, N. Y., was presented with a gold medal for his pioneer work with von Perquit on allergy. Among those taking part in the program were: Dr. George Waldbott, F.A.C.P., Detroit, Mich.; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio; Dr. Oscar Swineford, Jr., F.A.C.P., University, Va.; Dr. Theodore Squier, F.A.C.P., Milwaukee, Wis.; Dr. John M. Sheldon (Associate), Ann Arbor, Mich.; Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.; Dr. Carl D. Figley, F.A.C.P., Toledo, Ohio; Dr. J. Warrick Thomas, F.A.C.P., Cleveland, Ohio; Dr. Homer E. Prince, F.A.C.P., Houston, Tex.; Dr. Carl Way (Associate), Akron, Ohio; Dr. Frank A. Simon, F.A.C.P., Louisville, Ky.; and Dr. C. B. Bohner, F.A.C.P., Indianapolis, Ind., who was a member of the local committee on arrangements.

Dr. Maurice J. Dattelbaum, F.A.C.P., Brooklyn, N. Y., President of the Medical Society of the County of Kings, was honored at a dinner given by his friends on January 28, 1941.

On January 24, 1941, Dr. William H. Lohman, F.A.C.P., Brooklyn, N. Y., conducted the Scientific Session at the 29th meeting of the Brooklyn Society of Internal Medicine.

Dr. H. Beckett Lang, F.A.C.P., Albany, N. Y., has been appointed Superintendent of the Buffalo State Hospital. He was also recently appointed Lecturer in Social Psychiatry at the Millard Fillmore School of Social Work, University of Buffalo, and Lecturer in Psychiatry at the University of Buffalo Medical School.

Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill., spoke before the Schuyler and Cass County physicians at the Beardstown (Ill.) Hospital on January 8, 1941, on "Influenza and Respiratory Diseases" at the request of the Educational Committee of the Illinois State Medical Society.

Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., was the guest speaker at a recent meeting of the Wisconsin Anti-Tuberculosis Association held in Madison, Wis. Dr. Amberson spoke on "Diagnosis of Pulmonary Tuberculosis" and "Principles of Treatment of Tuberculosis."

Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., recently addressed the Polk County Medical Society at Webster, Wis., on "Vitamin K in Cases of Liver Depletion with and without Jaundice."

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., delivered the eighth E. Starr Judd Lecture at the University of Minnesota, January 15, 1941. His subject was "The Mechanisms of Gastric Secretion."

Dr. Edgar Mayer, F.A.C.P., New York, N. Y., spoke on "Tuberculosis in the Army under Present Epidemiologic Conditions" at the meeting of the New York State Chapter of the American College of Chest Physicians, January 17, 1941.

Dr. William J. Kerr, F.A.C.P., San Francisco, Calif., Professor of Medicine at the University of California Medical School, has been elected an honorary member of the Liga Argentina contra el Reumatismo, Buenos Aires.

Among those who conducted seminars at the Delaware State Hospital, Farnhurst, Del., November 24-26, and December 2-5, 1940, were:

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., "Psychiatry";
Dr. Charles W. Dunn, F.A.C.P., Philadelphia, Pa., "Endocrinology."

The Wisconsin State Board of Health and The Industrial Nurses of Wisconsin sponsored a symposium on "Industrial Public Health Nursing Services" in Milwaukee, Wis., February 20-22, 1941. Dr. William S. Middleton, F.A.C.P., Madison, Wis., presided at one of the sessions and Dr. Norbert Enzer, F.A.C.P., Milwaukee, spoke on the "Relationship of Cardio-Vascular Diseases to Accidents." Dr. Elston L. Belknap, F.A.C.P., Milwaukee, conducted a tour of inspection of several industrial plants.

Dr. John Walter Torbett, Sr., F.A.C.P., Marlin, Tex., has written in addition to his scientific articles, several books of poems of which his latest, "Practical Poems for Daily Use," has just been presented to the College Library of Publications by Members. This volume is a successor to "Joytown Jingles," "Pastime Poems," and "Centennial Songs." The present volume has been published by the Methodist Orphans' Home at Waco, Tex. The poems are devoted to the homely virtues of faith, hope, cheer, happiness and friendship, so representative of the author.

ERRATUM: Page 1139, January 1941 ANNALS, Table I, figures given as "No. of Cases 36, Mortality 60%" should read "No. of Cases 26, Mortality 84.6%."

OBITUARIES

DR. ROGER BROOKE

Dr. Roger Brooke, F.A.C.P., Brigadier General, U. S. Army, died at the Walter Reed General Hospital in Washington on December 18, 1940, of a heart ailment. He was born at Sandy Spring, Maryland, on June 14, 1878; the son of Roger and Louisa (Thomas) Brooke. After graduating from the George School at Newton, Pa., he entered the medical school of the University of Maryland, in Baltimore, where he graduated in 1900. He joined the medical corps of the Army on June 29, 1901, as a first lieutenant, passed through the various grades and was appointed a brigadier general on January 29, 1938. After graduating from the Army Medical School in the class of 1902 he had a tour of duty in the Philippines. Other early service included duty at Fort Bayard, N. M., at the Letterman General Hospital in San Francisco, at Fort Leavenworth, Kansas, and as attending surgeon in Washington. He spent the period of the World War in instruction work, serving from September 1917 to December 1918, first as senior instructor and later as commanding officer of the Medical Officers Training Camp at Camp Greenleaf, Georgia, where 10,000 officers and 70,000 enlisted men were prepared for service with the armed forces. For this service he was awarded the Distinguished Service Medal.

Later tours of duty included the office of The Surgeon General where he was chief of the tuberculosis section, division of medicine; the Veterans' Bureau, as chief medical consultant; at Gorgas Hospital in the Canal Zone, and at Fort Sam Houston, Texas, where he was commanding officer of the large station hospital. Brought again to the office of The Surgeon General in 1935 he was placed in charge of the professional service division. While on this duty he was promoted to brigadier general and sent to the command of Letterman General Hospital. He was later transferred to the post of commandant of the Medical Field Service School at Carlisle Barracks, Pa., his station at the time of his death.

Early in his army career, General Brooke interested himself in internal medicine and became well recognized as one of the foremost in that field that the corps has produced. Well versed in the study of tuberculosis from his early service at Fort Bayard, he instituted the overseas recruit depot at Fort Slocum, N. Y. in 1935, the first routine examination of the chest by roentgen-ray in the military service. He was a Fellow of the American College of Surgeons, and of the American College of Physicians, a member of the American Medical Association, the American Society of Tropical Medicine, the National Tuberculosis Association, and the Association of Military Surgeons of the United States. He contributed a number of articles to the pages of the *Military Surgeon* and to other medical journals.

General Brooke was married in 1905, at Baltimore, to Grace M. Macomb of that city, who, with a son, Roger, of San Francisco, survives him.

In the death of General Brooke the medical corps loses one of its exceptional students of medicine, one whose interest in the advances of his profession never flagged from the day of his graduation. He had a gift of vision of the possibilities of disease prevention. He was quiet spoken, gentle in manner, modest and unassuming in the exercise of his great talents. He leaves a host of devoted friends who will long remember him for his notable qualities and for the simple strength of his character.

The funeral services were held on December 20, 1940, at the Fort Myer Chapel, the Rev. Ivan L. Bennett, Chaplain, U. S. Army, officiating. Burial was in Arlington Cemetery.

JAMES M. PHALEN,
Colonel, U. S. Army (Retired).

DR. EDGAR A. HINES

In the death of Edgar Alphonso Hines, F.A.C.P., of Seneca, S. C., on Nov. 27, 1940, South Carolina lost a faithful, competent and indefatigable servant and organized medicine a devoted adherent.

Dr. Hines was born at Goldsboro, N. C., November 19, 1867. He attended Clemson College (S. C.) as a special student in chemistry and received his M.D. degree from the Medical College of the State of South Carolina in 1891. Dr. Hines served on the staff of Oconee County Hospital; was a member of the faculty of Southern Pediatric Seminar, and served one year as extramural lecturer on pediatrics at the Medical College of the State of South Carolina. He was vice chairman of the State Board of Health and one of the founders of the Board's bureau of child hygiene. During 1915 he was superintendent of the Anderson County Hospital. He was secretary of the South Carolina Medical Association and editor-in-chief of the *Journal of the South Carolina Medical Association* for many years. Dr. Hines was a Fellow of the American Medical Association and a member of the House of Delegates of this Association from 1910 to 1928 and from 1930 to 1940, and a Fellow of the American College of Physicians since 1924. He was a member and past president of the South Carolina Pediatric Society and the Piedmont Postgraduate Clinical Assembly; member of the American Academy of Pediatrics and diplomate of the American Board of Pediatrics; a member of the International Congress of School Hygiene and in 1913, session chairman of the Congress in Buffalo. He was also a member of the Oconee County Medical Society, South Carolina Medical Association, South Carolina Pediatric Society, South Carolina Hospital Association, Southern Medical Association, American Public Health Association and American Medical Editor's Association. He was Chairman of the Committee on Medical Preparedness for South Carolina.

Dr. Hines never ceased to be a student and inquirer and to the moment

of his sudden death was enthusiastically interested in furthering the best in medicine. With all, a kindly, unassuming man of many friends and attachments, his passing leaves a vacancy not easily or soon to be filled.

KENNETH M. LYNCH, M.D., F.A.C.P.,
Governor for South Carolina

DR. ROBERT TORREY

Dr. Robert G. Torrey, F.A.C.P., former President of the Medical Board of the Philadelphia General Hospital, died at his home at 1716 Locust Street, Philadelphia, on January 11, 1941.

Dr. Torrey was born in Richmond, Virginia, July 12, 1873, and received his M.D. degree from the University of Pennsylvania School of Medicine in 1906.

He had been Visiting Physician at the Philadelphia General Hospital since 1916, and for many years was Physician at the Medical Dispensary of the University Hospital, Physician at the Pennsylvania State Tuberculosis Dispensary, and Visiting Physician at St. Mary's Hospital.

Since 1916 Dr. Torrey had been Associate in Medicine at the University of Pennsylvania School of Medicine, and since 1931, Professor of Medicine at the Woman's Medical College of Pennsylvania.

He was elected to Fellowship in The American College of Physicians in 1923; was a member of The Philadelphia County Medical Society; the American Medical Association; the American Rheumatism Association, the American Heart Association; and the Racquet Club.

Dr. Torrey is survived by his wife, Mrs. Florence Smith Torrey; two sons, Robert D. and Philip C. Torrey; three brothers, Donald F., James E., and Arthur M. Torrey, and a sister, Miss Gertrude Torrey.

In addition to his high standing in the medical profession, particularly among his colleagues on hospital staffs and at the Woman's Medical College, Dr. Torrey had a large circle of close friends. His passing is a great loss to the profession of Philadelphia, his family and his intimates.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. HARRY E. WELCH

Dr. Harry E. Welch, a Fellow of the American College of Physicians since 1921, died in Youngstown, Ohio, on August 12, 1940, at 79 years of age.

Dr. Welch was born near the Mahoning River "by the light of the Falcon furnace"—Youngstown, a town of only 4,000 persons at that time. He was graduated from Rayen School there and during vacation periods and after school he filled-in as a steel worker.

In October of 1882 he matriculated at Western Reserve University, and

in 1886 after being graduated from the Western Reserve University School of Medicine he enjoyed a rare privilege for students of those days—he went abroad to study in Vienna, London and Berlin. Special attention was given to microscopy and pathology.

In 1887 he began the practice of medicine in Youngstown and in 1891 became Coroner of that city. A year later he was appointed Health Officer. His work in that capacity was so efficient that many times the City of Youngstown was especially designated as a healthful city.

For many years Dr. Welch conducted a medical service at the Youngstown Hospital and also served as a member of the Board of Trustees of this hospital. He served as local physician for the Erie Railroad for a period of forty years. He was a firm believer in organized medicine and maintained his affiliation with the American Public Health Association.

Dr. Welch had a keen appreciation for clinical medicine and his Sunday morning discussions in the staff room at the hospital were enjoyed by many of his professional friends for years. His great effort in establishing an outstanding sanitary community in Youngstown will always be remembered, not only by the medical profession but also by the laity.

He was unassuming in character, staunch in his belief of principle and genuine in his love for the public welfare. His passing leaves a void difficult to fill but a reputation we all could well emulate.

A. B. BROWER, M.D., F.A.C.P.,

Governor for Ohio

DR. ROLAND BEATTY TUPPER

Dr. Roland Beatty Tupper was born in Fresno, Calif., on July 26, 1886, and was graduated from Cooper Medical College in 1910. He served as intern at St. Luke's Hospital of San Francisco and later was a member of the staff of that institution. While a resident of San Francisco, he served as Assistant Clinical Professor of Medicine at Stanford University School of Medicine. During the World War he was a member of the Stanford Group in Scotland at the U. S. Naval Base Hospital.

Soon after the World War Dr. Tupper located in Fresno, where he was Chief of the Men's Medical Service at the General Hospital of Fresno County, which position he held until the time of his death. He was also a member of the staff of the Burnett Sanitarium. He was a Fellow of the American Medical Association, a member of the American College of Chest Physicians and an Associate of the American College of Physicians.

Dr. Tupper was held in high esteem as a consultant, as well as a practitioner of internal medicine, and his death on October 30, 1940, was a distinct loss to the profession and to his community.

W. E. R. SCHOTTSTAEDT, M.D., F.A.C.P.,

Fresno, California

PROGRAM
TWENTY-FIFTH ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
BOSTON, MASS.

April 21-25, 1941

GENERAL SESSIONS AND LECTURES

James D. Bruce, President

BOSTON COMMITTEE ON ARRANGEMENTS

William B. Breed, General Chairman

F. Gorham Brigham

Earle M. Chapman

Reginald Fitz

Dwight O'Hara

Howard B. Sprague

Soma Weiss

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Reginald Fitz, Chairman

Lewis M. Hurxthal, Vice Chairman.....	Lahey Clinic
Joseph C. Aub....	Peter Bent Brigham and Collis P. Huntington Memorial Hospitals
Elliott P. Joslin.....	New England Deaconess Hospital
Chester S. Keefer.....	Massachusetts Memorial Hospitals
James H. Means.....	Massachusetts General Hospital
Cadis Phipps.....	Boston City Hospital
Joseph H. Pratt.....	Boston Dispensary
Abraham Rudy.....	Beth Israel Hospital

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Earle M. Chapman, Chairman

Robert T. Monroe, Vice Chairman

Lowrey F. Davenport

Alexander Marble

Herman C. Petterson

COMMITTEE ON ENTERTAINMENT

F. Gorham Brigham, Chairman

Conrad Wesselhoef, Vice Chairman

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Walter Bauer, Vice Chairman

William B. Castle

George R. Minot

James M. Faulkner

James P. O'Hare

Joseph R. Frothingham

William R. Ohler

Robert W. Wilkins

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Mrs. William B. Breed

Mrs. James H. Means

Mrs. F. Gorham Brigham

Mrs. George R. Minot

Mrs. Reginald Fitz

Mrs. B. Harrison Ragle

Mrs. Francis C. Hall

Mrs. Fritz B. Talbot

Mrs. Albert A. Hornor

Mrs. James H. Townsend

Mrs. Elliott P. Joslin

Mrs. Thomas V. Urmy

Mrs. Roger I. Lee

Mrs. Soma Weiss

Mrs. Conrad Wesselhoeft

HONORARY COÖPERATING COMMITTEE

C. Sidney Burwell, Dean, Harvard Medical School

A. Warren Stearns, Dean, Tufts College Medical School

Bennett F. Avery, Dean, Boston University School of Medicine

Walter G. Phippen, President, Massachusetts Medical Society

David Cheever, President, Boston Medical Library

Albert A. Hornor, President, Suffolk District Medical Society

Frank H. Lahey, President-Elect, American Medical Association

John J. Reddy, Colonel, Medical Corps, U. S. Army, First Corps Area Army Base

John L. Neilson, Captain, Medical Corps, U. S. Navy, First Naval District, Navy Yard

Paul J. Jakmauh, State Commissioner of Public Health
 Clifton T. Perkins, State Commissioner of Mental Health
 G. Lynde Gately, Commissioner of Public Health for Boston
 Grover A. Kempf, Medical Officer in Charge, U. S. Marine Hospital

NEW ENGLAND GOVERNORS FOR THE AMERICAN COLLEGE OF PHYSICIANS

Eugene H. Drake.....	Maine
Robert B. Kerr.....	New Hampshire
Paul K. French.....	Vermont
Alexander M. Burgess.....	Rhode Island
Charles H. Turkington.....	Connecticut

GENERAL INFORMATION

Boston Headquarters

Hotel Statler, Park Square at Arlington Street

Hotel Statler will be headquarters for Officers, Regents, Governors and members of the College, as well as general headquarters for registration, technical exhibits, general scientific sessions, special lectures and panel discussions.

The Copley Plaza Hotel, three blocks removed from Hotel Statler, has graciously made available to the College one of its public halls in which one series of panel discussions will be conducted daily.

List of Boston Hotels	Blocks from Hotel Statler	Rates per day, with private bath	
		Single Room	Double Room
HOTEL STATLER.....		\$3.50-8.00	\$5.00-12.00
HOTEL COPLEY PLAZA.....		4.00-6.00	6.00-12.00
Bradford Hotel.....	3½	3.00-4.00	4.50- 6.00
*Copley Square Hotel.....	4	3.00-3.50	5.00- 6.00
Kenmore Hotel.....	14	3.50-5.00	5.00- 7.00
*Lenox Hotel.....	4	2.75-3.50	3.50- 6.00
Lincolnshire Hotel.....	7	3.00-4.00	5.00- 7.00
Myles Standish.....	14	3.00-3.50	4.00- 5.00
Puritan Hotel.....	11	4.00-5.00	5.00- 7.00
Ritz-Carlton Hotel.....	2½	5.00-8.00	8.00-10.00
Sheraton Hotel.....	15	3.00-3.50	4.00- 6.00
Somerset Hotel.....	12	3.50-4.00	6.00- 7.00
*Touraine Hotel.....	3	3.50-5.50	5.00- 7.50
Victoria Hotel.....	4	2.50-4.00	4.00- 6.00
Westminster Hotel.....	2	2.50-3.00	4.00- 5.00

* Rooms without bath also are available at lower rates than quoted.

Rates for suites and for large rooms accommodating three or four persons furnished upon application.

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates quoted are, in some instances, only for this occasion.

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1941 (dues, if not paid previously, may be paid at the Registration Bureau).
- (b) All newly elected members.
- (c) Medical students (fourth year only) pursuing courses at any approved medical school in Massachusetts (Harvard Medical School, Boston University School of Medicine, Tufts College Medical School), without registration fee, upon presentation of matriculation cards, or other evidence of

registration at these institutions; exhibits, morning lectures, general sessions.

- (d) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, panel discussions and general sessions.
- (e) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
- (f) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open on the mezzanine floor of the Hotel Statler on Sunday, April 20, from 2:30 to 5:00 in the afternoon, and from 7:00 to 9:00 in the evening. Thereafter the Registration Bureau will be open daily, 8:30 a.m. to 6:00 p.m., Monday to Friday, April 21–25.

REGISTRATION BLANKS FOR ALL CLINICS AND PANEL DISCUSSIONS will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session. Advance reservations for clinics and panels can be made for members only.

BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Hotel Statler.

TRANSPORTATION—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Physicians should consult their local ticket agents.

Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting. A map will be published in the formal program on which will be clearly indicated the headquarters, and the clinics and medical schools at which morning clinics and demonstrations will be held. Transportation to these points will be offered in three forms:

(1) A general bus transportation ticket on sale at the Registration Bureau, which will entitle the holder to bus transportation each morning throughout the week at 8:45 a.m. (Columbus Street exit of the Hotel Statler, or the Huntington Avenue entrance of the Hotel Copley Plaza) to go to any clinic or demonstration point and return from that same point at 12:00 m.

(2) Taxicabs—The Checker Taxicab Company and the Town Taxicab Company have guaranteed the following rates:

From Hotel Statler to:	Checker	Taxis	Town
Copley Plaza	\$.25		\$.30
Back Bay Station30		.35
Trinity Place Station30		.30
South Station45		.45
North Station65		.55
Massachusetts Memorial Hospital50		.50
City Hospital55		.50
Peter Bent Brigham Hospital75		.65
Good Samaritan Hospital70		.70
Children's Hospital70		.65
Beth Israel Hospital70		.65
Psychopathic Hospital75		.75
N. E. Deaconess Hospital80		.75
Haynes Memorial Hospital	1.30		1.30
Massachusetts General Hospital50		.50
Joseph Pratt Diagnostic Hospital40		.40

(3) Subway—The subway entrance is just a few yards in front of the Hotel Statler entrance. Subway trains reach all points.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5:00 p.m., Thursday, April 24, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, and the annual reports of the Secretary-General, Executive Secretary and Treasurer will be presented. The President-Elect, Dr. Roger I. Lee, Boston, Mass., will be inducted into office.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled, as indicated. Special meetings will be announced and posted.

A *dinner meeting* of the Board of Regents and of the Board of Governors will be held at the Hotel Statler, Parlor A, mezzanine floor, Sunday evening, April 20, at seven o'clock.

COMMITTEE ON CREDENTIALS

Sunday, April 20, 9:00 a.m. Hancock Room, mezzanine floor, Hotel Statler

BOARD OF REGENTS

Hancock Room, mezzanine floor, Hotel Statler

Sunday, April 20, 2:30 p.m.

Tuesday, April 22, 12:00 m.*

Friday, April 25, 12:00 m.*

BOARD OF GOVERNORS

Hancock Room, mezzanine floor, Hotel Statler

Monday, April 21, 5:00 p.m.

Wednesday, April 23, 12:00 m.*

SPECIAL FEATURES

MONDAY, APRIL 21, 1941

THE ANNUAL SMOKER—Directly following the last presentation of the second General Session on Monday evening in the same hall (Statler Ballroom), the so-called Smoker will be held. Though plenty of tobacco will be available, the emphasis this year will be placed on food, fun, friendship, beer and music. There will be no formal vaudeville or floor show, but ample opportunity will be provided for renewing old acquaintances and establishing new ones. Oyster bars will be prominent, and for those allergic to seafoods, a collation of orthodox items for satisfaction of the inner man will be available. A small mobile orchestra (Ruby Newman's) will provide appropriate informal music to accompany such barber shop tendencies as may crop up, but there will be no organized community singing. Perhaps a few short moving picture presentations will be offered—nothing, however, which is likely to tax the intellect.

In short, Monday will provide a modified free evening. Your Committee believes that the Monday evening gathering can be set up to further the social aspects of the College without detracting from the entertainment value of the Annual Smoker.

Fellows and Associates, local and visiting physicians and the technical exhibitors are invited to attend the Smoker as guests of the College. The registration badge is all that will be needed for identification.

* Buffet luncheon served.

TUESDAY, APRIL 22, 1941

SYMPHONY CONCERT—8:45 p.m., Symphony Hall, corner Massachusetts Avenue and Huntington Avenue—Largely through the good offices of Dr. Roger I. Lee, our President-Elect, Dr. Serge Koussevitzky, Conductor of the Boston Symphony Orchestra, has invited the members of the College and their guests to Symphony Hall on Tuesday evening.

Your Committee knows that this nationally famous orchestra and its conductor need no introduction to the members of the College—and that they will consider this invitation in the light of a great honor. The only way in which we can show our appreciation is to see that there is a full house on that night, which should not be difficult under the circumstances.

It is suggested that those members who are planning dinner parties schedule them for Tuesday evening at 6:30, so that ample time will be available for comfortable dining before the doors of Symphony Hall close at nine o'clock.

Though the actual musical program has not been arranged, our experience with Dr. Koussevitzky as a program maker makes us confident that, as far as entertainment goes, the concert will be the high-light of the meeting.

All connected with the College meeting, members, guests, exhibitors and friends, are included in this invitation. They may bring local friends—in fact, they are urged to do so. Tickets will be distributed at the Hotel Statler on Monday and Tuesday. Opportunity to reserve seats ahead of time will be afforded members at the time of distribution of the final Program in February.

WEDNESDAY, APRIL 23, 1941

CONVOCATION OF THE COLLEGE—8:30 p.m., Ballroom, Hotel Statler. All members of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in Parlor "A" on the mezzanine floor at 7:45 o'clock, preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation promptly at 8:30. It is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation ceremony will include the President's Address and the Convocational Address which this year will be delivered by Dr. James Alex. Miller, F.A.C.P., Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons; former President of the American College of Physicians and former President of the New York Academy of Medicine. The award of the John Phillips Memorial Medal will be made to Dr. William C. Stadie, of Philadelphia, and the recipients of the Research Fellowships of the College for 1941 will be announced. The newly elected Fellows will be presented by the Secretary-General and, after subscribing to the Fellowship Pledge, will be inducted by the President.

The President's Reception and Dance will follow immediately after the Convocation, and will be held in the Ballroom of the Hotel Statler. At the end of the Convocation exercises, the audience is requested to leave the Ballroom for approximately twenty minutes while the Hall is rearranged for the Reception and Dance. All members and their guests are requested to pass along the receiving line. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Music for the Reception and Dance will be furnished by Ruby Newman and his orchestra.

THURSDAY, APRIL 24, 1941

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Ballroom of the Hotel Statler at eight o'clock. Dr. William B. Breed, General Chairman of the Twenty-fifth Annual Session of the College, will be the Toastmaster. The address of the evening will be delivered by Earnest Albert Hooton, Ph.D., B.Litt., Sc.D., Professor of Anthropology, Harvard University. His subject will be "Hip-Hip-Hip-pocrates, or An Anthropological Cheer for Medicine."

All members of the College, physicians of Boston and visitors attending the Session with their families and friends, are cordially invited. Table reservations for groups may be arranged. Music will be furnished by Ruby Newman and his orchestra. Tickets should be purchased at the Registration Bureau by Wednesday afternoon—price, \$4.00.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The wives of the Boston members of the College cordially invite all the visiting women at the College meeting in Boston to participate in the special program of entertainment arranged for them. A postal card will be sent with the final Program, in order that advanced intentions may be indicated.

The visiting women are asked to register immediately upon arrival in Boston at their Headquarters in Room 419 of the Hotel Statler. There they will receive a program of entertainment and information about theaters, restaurants, stores and places of interest in and around Boston.

It is necessary to make reservations for some of the events on the Ladies' Program.

MONDAY, APRIL 21, 1941

Morning: Registration, Room 419, Hotel Statler.

Afternoon: 4:00 to 6:00 p.m. Welcoming Tea at the Women's City Club, 40 Beacon Street.

Evening: Free for theater, movies, bridge.

TUESDAY, APRIL 22, 1941

Morning: Free.

Afternoon: 1:15 p.m. Buses leave Hotel Statler for short visit to Harvard University with guide service through Harvard Yard, the Memorial Chapel, Widener Library, the Fogg Museum, the Peabody Museum (glass flowers) and one of the Houses.

3:30 p.m. Buses leave Cambridge for the home of Mrs. Arthur Lyman in Waltham where we are to be her guests at Tea.

4:30 to 5:00 p.m. Buses return to Hotel Statler. Bus fare, \$1.00.

Evening: 9:00 p.m. Concert at Symphony Hall by Boston Symphony Orchestra for the members of the American College of Physicians and their wives, at the invitation of Dr. Serge Koussevitzky, Conductor.

WEDNESDAY, APRIL 23, 1941

Morning: Free.

Afternoon: 1:30 p.m. Buses leave for the Isabella Gardner Museum and conducted tour of the Palace, followed by music and tea in the Tapestry Room as guests of the College. Return at 4:30 to Hotel Statler. Bus fare, \$.50.

Evening: 8:30 p.m. Convocation, President's Reception and Dance in the Ballroom, Hotel Statler. Ruby Newman and orchestra.

THURSDAY, APRIL 24, 1941

Morning: Free.*Afternoon:* 1:00 p.m. Lunch and Fashion Show by Hickson in the main dining room, Hotel Ritz-Carlton. Luncheon a la carte (\$1.25 minimum).*Evening:* 8:00 p.m. Annual Banquet of the College in the Ballroom, Hotel Statler. Ruby Newman and orchestra.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the mezzanine floor of the Hotel Statler. From the accompanying diagram it will be noted that the Exhibit is widely extended because of the facilities available, but actually the total exhibit space is not as great as customary. Members are urged to familiarize themselves with the Exhibit layout and to make it a point to visit all the exhibitors, but especially is it requested that the attending physicians make a particular effort to visit the exhibits, numbers 1 to 24, which are somewhat removed from the main course of travel.

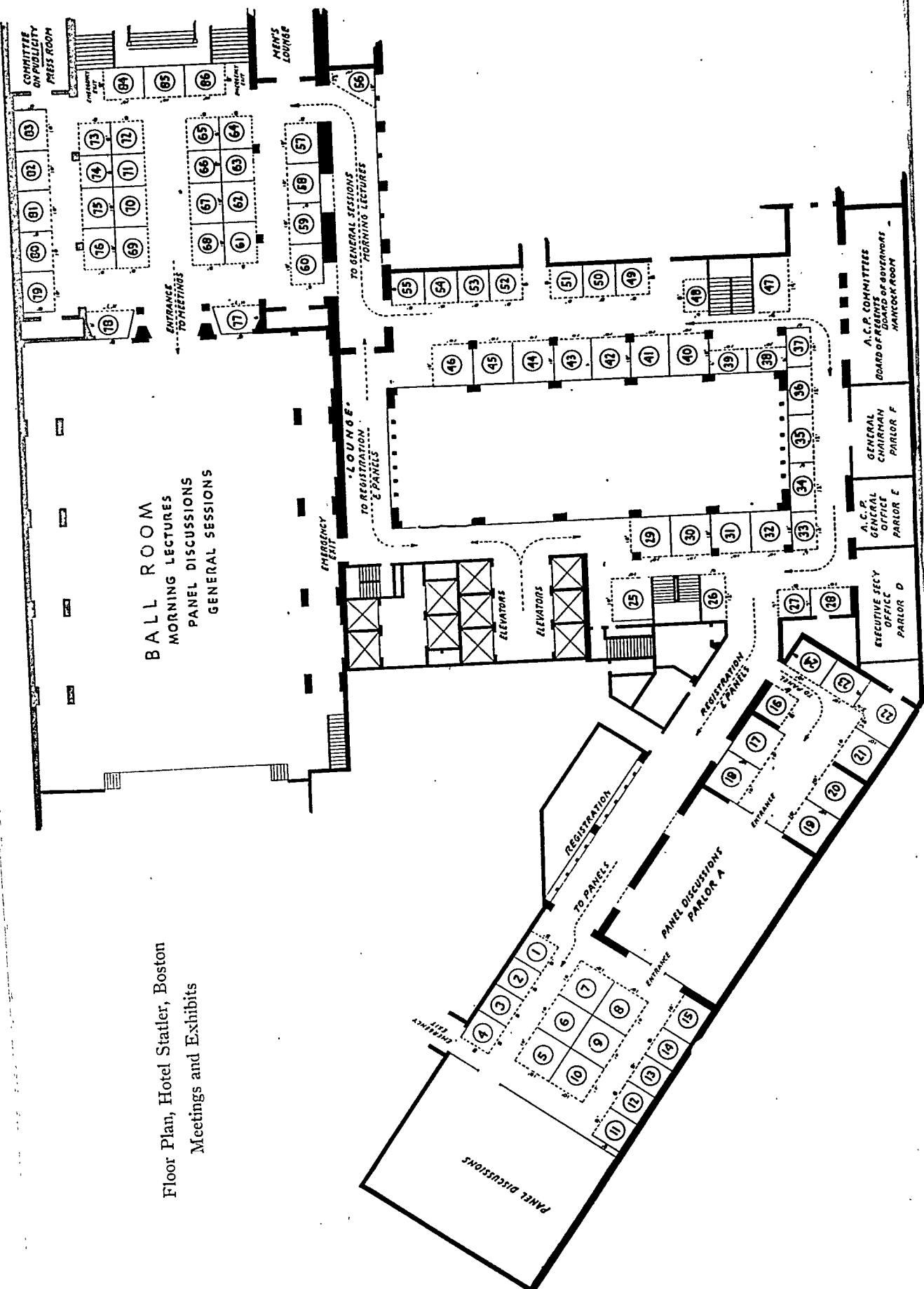
The College has put forward an organized effort to raise the standards of the technical exhibits. All irrelevant products have been eliminated and only firms are invited who shall present a group of approved products of scientific interest to Internal Medicine and its allied specialties. Members of the College will readily distinguish the difference between this Exhibit and the general medical exhibit elsewhere where frequently all sorts of irrelevant products are displayed, "catch-penny" exhibits accepted, and where methods of high-pressure selling are common. The Exhibit sponsored by our College warrants the respect and interest of every attending physician. Here conveniently assembled will be the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice. These exhibitors and their displays merit your special attention, not only because of their educational value, but because of their contributions to the support of the Annual Sessions of the College.

Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

LIST OF EXHIBITORS

	<i>Booth No.</i>
White Laboratories, Inc., Newark, N. J.	1
J. H. Emerson Company, Cambridge, Mass.	2-3
Gradwohl Laboratories, St. Louis, Mo.	4
The Wm. S. Merrell Company, Cincinnati, Ohio	5
Hanovia Chemical & Mfg. Company, Newark, N. J.	6
Jones Metabolism Equipment Co., Chicago, Ill.	7
Carnation Company, Oconomowoc, Wis.	8-9
Unassigned	10
Abbott Laboratories, North Chicago, Ill.	11
Duke Laboratories, Inc., Stamford, Conn.	12
American Heart Association, New York, N. Y.	13
Mallinckrodt Chemical Works, St. Louis, Mo.	14
Sandoz Chemical Works, Inc., New York, N. Y.	15
S. H. Camp & Company, Jackson, Mich.	16
Schering Corporation, Bloomfield, N. J.	17
The New York Medical Exchange, New York, N. Y.	18
Ciba Pharmaceutical Products, Inc., Summit, N. J.	19-20
Cameron Heartometer Co., Chicago, Ill.	21
Ritter Equipment Co., Inc., Rochester, N. Y.	22
American Hospital Supply Corporation, Chicago, Ill.	23

Floor Plan, Hotel Statler, Boston
Meetings and Exhibits



Kellogg Company, Battle Creek, Mich.	24
Mead Johnson & Company, Evansville, Ind.	25
Medical Case History Bureau, New York, N. Y.	26
Laboratoire Nativelle, New York, N. Y.	27
Cambridge Instrument Co., Inc., New York, N. Y.	28
General Electric X-Ray Corporation, Chicago, Ill.	29-30
Paul B. Hoeber, Inc., New York, N. Y.	31
John Wyeth & Brother, Inc., Philadelphia, Pa.	32
Davies, Rose & Company, Ltd., Boston, Mass.	33
Year Book Publishers, Chicago, Ill.	34
E. R. Squibb & Sons, New York, N. Y.	35
Williams & Wilkins Company (William Wood Books), Baltimore, Md.	36
Parke, Davis & Company, Detroit, Mich.	37
Eli Lilly and Company, Indianapolis, Ind.	38-39-40
Frederick Stearns and Company, Detroit, Mich.	41
Allergia Products Co., Newton, Mass.	42
The Medical Bureau, Chicago, Ill.	43
Winthrop Chemical Company, Inc., New York, N. Y.	44
Lea & Febiger, Philadelphia, Pa.	45
The E. L. Patch Co., Boston, Mass.	46
Picker X-Ray Corporation, New York, N. Y.	47
W. A. Baum Co. Inc., New York, N. Y.	48
The Macmillan Company, New York, N. Y.	49-50
The Arlington Chemical Company, Yonkers, N. Y.	51
Vegex, Incorporated, New York, N. Y.	52
The Blakiston Company, Philadelphia, Pa.	53
J. B. Lippincott Company, Philadelphia, Pa.	54-55
LaMotte Chemical Products Company, Baltimore, Md.	56
Sanborn Company, Cambridge, Mass.	57
Taylor Instrument Companies, Rochester, N. Y.	58
Merck & Co. Inc., Rahway, N. J.	59-60
W. B. Saunders Company, Philadelphia, Pa.	61
The G. F. Harvey Company, Saratoga Springs, N. Y.	62
D. Appleton-Century Company, Inc., New York, N. Y.	63
F. A. Davis Company, Philadelphia, Pa.	64
Riedel-de Haen, Inc., New York, N. Y.	65
Smith, Kline & French Laboratories, Philadelphia, Pa.	66-67
The Muller Laboratories, Baltimore, Md.	68
Devereux Schools, Devon, Pa.	69
H. J. Heinz Co., Pittsburgh, Pa.	70-71
Bilhuber-Knoll Corp., Orange, N. J.	72
Gerber Products Company, Fremont, Mich.	73
S. M. A. Corporation, Chicago, Ill.	74
Oxford University Press, New York, N. Y.	75
The Maltine Company, New York, N. Y.	76
Cameron Surgical Specialty Co., Chicago, Ill.	77
Warren E. Collins, Inc., Boston, Mass.	78
The C. V. Mosby Company, St. Louis, Mo.	79
Becton, Dickinson & Co., Rutherford, N. J.	80-81
Kalak Water Co. of New York, Inc., New York, N. Y.	82
Ayerst, McKenna & Harrison (U. S.) Ltd., Montreal, Que.	83
Lederle Laboratories, Incorporated, New York, N. Y.	84-85-86

OUTLINE OF THE BOSTON SESSION
Hotel Statler events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 21	April 22	April 23	April 24	April 25
9:00 a.m. to 11:30 a.m.	Morning free Registration, Exhibits, etc.	Hospital Clinics Morning Lectures (9:30- 11:30)	Hospital Clinics Morning Lectures (9:30- 11:30)	Hospital Clinics Morning Lectures (9:30- 11:30)	Hospital Clinics Morning Lectures (9:30- 11:30)
12:00 m. to 1:15 p.m.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
1:15 p.m. to 2:15 p.m.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:15 p.m. to 5:00 p.m.	1st General Session	3d General Session	4th General Session	5th General Session Annual Business Meeting	6th General Session
5:00 p.m. to 8:00 p.m.	Dinner	Dinner	Dinner		
8:00 p.m. to 11:00 p.m.	2d General Session followed by SMOKER	8:45 Symphony Concert	CONVOCATION, followed by President's Reception	ANNUAL BANQUET	

GENERAL SESSIONS

The program of the General Sessions has been developed in accordance with suggestions from a large number of members with widely diversified interests. Inasmuch as these suggestions fell into certain divisions, it seemed appropriate as well as expedient to set up most of the General Sessions in the form of symposia.

The Session on Military Medicine and that on Nutritional and Metabolic Diseases seem fully justified by the necessities of the National Defense Program and the preparation for probable needs of the civilian population consequent upon a diversion from peace time activities. The Surgeons General of the Army, Navy and Public Health Services have graciously consented to be with us and present an accounting of progress in National preparedness.

That part of the General Sessions devoted to Education should serve to reaffirm the position of the College in this field, as well as to clarify its objectives.

GENERAL SESSIONS PROGRAM

Ballroom, Hotel Statler

FIRST GENERAL SESSION

Monday Afternoon, April 21, 1941

General Chairman William B. Breed, presiding

p.m.

2:15 Addresses of Welcome:

WILLIAM B. BREED, F.A.C.P., General Chairman, Twenty-fifth Annual Session, Boston, Mass.

WALTER G. PHIPPEN, President of the Massachusetts Medical Society.

FRANK H. LAHEY, President-Elect of the American Medical Association.

The Honorable MAURICE J. TOBIN, Mayor of Boston.

The Honorable LEVERETT SALTONSTALL, Governor of Massachusetts.

JAMES B. CONANT, President of Harvard University.

Response to Addresses of Welcome:

JAMES D. BRUCE, F.A.C.P., President of the American College of Physicians; Vice President in Charge of University Relations, University of Michigan; Ann Arbor, Mich.

3:30 INTERMISSION.

President James D. Bruce, presiding

4:00 The Responsibility of the Hospital Staff in Graduate Medical Education.

FRANK J. SLADEN, F.A.C.P., Lecturer in Postgraduate Medicine, University of Michigan; Physician-in-Chief of Henry Ford Hospital, Detroit, Mich.

4:20 The American Board of Internal Medicine as a Factor in Scholarship in American Medicine.

ERNEST E. IRONS, F.A.C.P., Clinical Professor of Medicine and Chairman of Department, Rush Medical College; Chairman, American Board of Internal Medicine; Chicago, Ill.

4:40 The Responsibility of the American College of Physicians for Postgraduate Training.

EDWARD L. BORTZ, F.A.C.P., Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine; Chairman, Advisory Committee on Postgraduate Courses, American College of Physicians, Philadelphia, Pa.

5:00 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, April 21, 1941

Presiding Officer

Roger I. Lee, F.A.C.P., Boston, Mass.

p.m.

- 8:00 Results in the Medical Management of Bleeding Ulcer.
T. GRIER MILLER, F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- 8:15 The Results of Surgical Treatment of Ulcerative Colitis.
HENRY W. CAVE (by invitation), Assistant Clinical Professor of Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.
- 8:30 Sinusitis and Bronchiectasis. A New Interpretation.
HERMAN H. RIECKER, F.A.C.P., Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.
- 8:45 The Value of Sternal Marrow Aspiration as a Method of Bone Marrow Biopsy.
ERNEST H. FALCONER, F.A.C.P., Clinical Professor of Medicine, University of California Medical School, San Francisco, Calif.
- 9:00 The Rôle of the Vertebral Veins in Metastatic Processes.
OSCAR V. BATSON (by invitation), Professor of Anatomy, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, Pa.
- 9:15 Fat Metabolism in Diabetes Mellitus.
WILLIAM C. STADIE (by invitation), Associate Professor of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- 9:40 ADJOURNMENT.

10:00 o'Clock

SMOKER

Ballroom, Hotel Statler

Program—Food, fun, friendship, refreshments and music. Admission by registration badge.

THIRD GENERAL SESSION

Tuesday Afternoon, April 22, 1941

Presiding Officer

Robert A. Cooke, F.A.C.P., New York, N. Y.

SYMPOSIUM ON DISEASES OF CIRCULATION

p.m.

- 2:15 William Withering. His Contribution to Medicine.
JONATHAN C. MEAKINS, F.A.C.P., Professor of Medicine, McGill University Faculty of Medicine, Montreal, Que., Canada.
- 2:40 Anticipation and Diagnosis of the Effort Syndrome (Irritable Heart).
JOHN T. KING, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.
- 3:00 Silent or Atypical Coronary Occlusion.
WILLIAM D. STROUD, F.A.C.P., Professor of Cardiology, University of

Pennsylvania Graduate School of Medicine, Philadelphia, Pa., and
JOSEPH A. WAGNER (by invitation), Morris W. Stroud, Jr., Fellow in
Cardiology, Pennsylvania Hospital, Philadelphia, Pa.

3:20 INTERMISSION.

4:00 The Chemotherapy of Sub-Acute Bacterial Endocarditis.

RALPH KINSELLA, F.A.C.P., Professor of Medicine, St. Louis University,
St. Louis, Mo.

4:20 Kidney Extract in the Treatment of Experimental and Clinical Hypertension.

IRVINE H. PAGE (Associate, A.C.P.), Director, Lilly Laboratory for Clinical Research, Indianapolis, Ind.

4:40 Physiology of the Early Manifestations of Left Heart Failure.

C. SIDNEY BURWELL, F.A.C.P., Research Professor of Clinical Medicine
and Dean of the Faculty of Medicine, Harvard Medical School, Boston,
Mass.

5:00 ADJOURNMENT.

FOURTH GENERAL SESSION

Wednesday, April 23, 1941

Presiding Officer

James G. Carr, F.A.C.P., Chicago, Ill.

SYMPOSIUM ON NUTRITIONAL AND METABOLIC DISEASES

p.m.

2:15 The National Nutrition Program.

RUSSELL M. WILDER, F.A.C.P., Professor of Medicine and Nutrition, and
Chief of Department of Medicine, University of Minnesota (Mayo
Foundation), Rochester, Minn.; Chairman, Committee on Food and
Nutrition, National Research Council, Washington, D. C.

2:35 Food Rationing in the Armed Forces.

LT. COL. PAUL LOGAN (by invitation), Quartermaster Corps, The Army
Industrial College, Washington, D. C.

2:55 Insulin and Protamine Zinc Insulin in the Management of Diabetes.

EDWARD H. MASON, F.A.C.P., Associate Professor of Medicine, McGill
University Faculty of Medicine, Montreal, Que., Canada.

3:15 Protein Derivatives as Factors in Allergy.

ROBERT A. COOKE, F.A.C.P., Assistant Professor of Clinical Medicine,
Cornell University Medical College, New York, N. Y.

3:35 INTERMISSION.

4:00 Chemistry of Vitamin K.

LOUIS F. FIESER (by invitation), Professor of Chemistry, Harvard Uni-
versity, Cambridge, Mass.

4:20 The Clinical Symptoms and Signs of Vitamin B Complex Deficiency.

WILLIAM H. SEBRELL, JR. (by invitation), Chief, Division of Chemo-
therapy, U. S. Public Health Service, Washington, D. C.

4:40 The Syndrome of Multiple Vitamin Deficiency.

V. P. SYDENSTRICKER, F.A.C.P., Professor of Medicine, University of
Georgia School of Medicine; Physician-in-Chief, University Hos-
pital, Augusta, Ga.

5:00 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 23, 1941

8:30 o'Clock

Ballroom, Hotel Statler

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. The President's Address.

James D. Bruce.

2. Presentation of Newly-Elected Fellows and Recital of the Pledge.

George Morris Piersol, Secretary-General.

3. Presentation of John Phillips Memorial Medal for 1940-41.

4. Announcement of Research Fellows of the College for 1941.

5. Convocational Address:

JAMES ALEXANDER MILLER, F.A.C.P., Former President of the American College of Physicians, New York, N. Y.

President's Reception

The Reception and Dance will follow one-half hour after the completion of this program, and will be held in the Ballroom of the Hotel Statler. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

FIFTH GENERAL SESSION

Thursday Afternoon, April 24, 1941

Presiding Officer

O. H. Perry Pepper, F.A.C.P., Philadelphia, Pa.

SYMPOSIUM ON MILITARY MEDICINE

p.m.

2:00 The United States Army.

SURGEON GENERAL JAMES C. MAGEE (Major General, M.C.), U.S.A.
(F.A.C.P.)

2:20 The United States Navy.

SURGEON GENERAL ROSS T. MCINTIRE (Rear Admiral, M.C.), U.S.N.
(F.A.C.P.).

2:40 The United States Public Health Service.

SURGEON GENERAL THOMAS PARRAN, U. S. Public Health Service
(F.A.C.P.).

3:00 Industrial Hygiene in the National Defense Program.

PAUL A. NEAL, U. S. Public Health Service (by invitation), and J. J.
BLOOMFIELD, U. S. Public Health Service (by invitation).

3:20 The Control of Infectious Diseases in Rapidly Mobilized Troops.

LT. COL. A. P. HITCHENS, M.C., U.S.A. (F.A.C.P.); Professor of Public
Health and Preventive Medicine, University of Pennsylvania School
of Medicine, Philadelphia, Pa.

3:40 INTERMISSION.

- 4:00 The Development of Plasma Preparations for Transfusions.
 MAX STRUMIA (by invitation), Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
- 4:20 Special Medical Service in the Defense Program.
 COMMANDER C. S. STEPHENSON, M.C., U.S.N. (By invitation.)
- 4:40 The Recruit's First Year.
 LT. COL. PATRICK S. MADIGAN, M.C., U.S.A. (F.A.C.P.).
- 5:00 ADJOURNMENT, to be followed immediately by

THE ANNUAL BUSINESS MEETING

All Masters and Fellows are urged to be present. Annual reports of the Secretary General, Executive Secretary and Treasurer will be presented; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. Roger I. Lee, Boston, Mass., will be inducted into office.

THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, 8:00 o'Clock

Ballroom, Hotel Statler

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: William B. Breed, F.A.C.P., Boston, Mass.

Address: "Hip-Hip-Hippocrates, or An Anthropological Cheer for Medicine."

Earnest Albert Hooton, Ph.D., B.Litt., Sc.D., Professor of Anthropology, Harvard University.

SIXTH GENERAL SESSION

Friday, April 25, 1941

Presiding Officer

Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md.

SYMPOSIUM ON INFECTIOUS DISEASES

p.m.

2:15 Influenza.

FRANK L. HORSFALL, JR. (by invitation), International Health Division, The Rockefeller Institute for Medical Research, New York, N. Y.

2:30 Rheumatic Heart Disease in Southern Climates.

GEORGE R. HERRMANN, F.A.C.P., Professor of Clinical Medicine, University of Texas School of Medicine, Galveston, Texas;

GEORGE M. DECHERD, JR. (F.A.C.P.), Associate Professor, University of Texas School of Medicine, Galveston, Texas, and

J. T. ROBERTS (by invitation), Assistant Professor, University of Texas School of Medicine, Galveston, Texas.

2:45 Management of Pneumonias Associated with Pneumococci of the Higher Numbered Types.

HOBART A. REIMANN (by invitation), Professor of Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

- 3:00 Mass Immunization against Typhus Fever.
R. E. DYER (by invitation), Chief, Division of Infectious Diseases, U. S. Public Health Service, Washington, D. C.
- 3:15 Screening for Tuberculosis in a Civilian Population by Fluorography.
BRUCE H. DOUGLAS (F.A.C.P.), Controller of Tuberculosis, Detroit Health Department, Detroit, Mich., and
CARL C. BIRKELO (by invitation), Detroit, Mich.
- 3:35 INTERMISSION.
- 4:00 Treatment of Cardiovascular Syphilis.
UDO J. WILE, F.A.C.P., Professor of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Mich.
- 4:15 Scarlet Fever Immunization.
JOHN A. TOOMEY, F.A.C.P., Professor of Clinical Pediatrics and Contagious Diseases, Western Reserve University School of Medicine, Cleveland, Ohio.
- 4:30 The Diagnosis and Management of Brucellosis.
WALTER M. SIMPSON, F.A.C.P., Director, Kettering Institute for Medical Research; Diagnostic Laboratories, Miami Valley Hospital, Dayton, Ohio.
- 4:45 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures are in response to increasing interest in fundamental problems and are planned to relate as closely as possible to the subject matter of the General Sessions.

They will be held daily, Tuesday through Friday, from 9:30 to 11:30 a.m., in the Ballroom of the Hotel Statler.

The lectures will be open to all members and guests of the College.

Admission by regular registration badge.

Tuesday Morning, April 22, 1941

Ballroom, Hotel Statler

Presiding Officer

D. Sclater Lewis, F.A.C.P., Montreal, Que.

a.m.

- 9:30 The Development and Present Status of the Precordial Electrocardiogram.
FRANK N. WILSON, F.A.C.P., Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.
- 10:30 Peripheral Circulation Failure Mechanisms.
CARL J. WIGGERS, F.A.C.P., Professor of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio.

Wednesday Morning, April 23, 1941

Ballroom, Hotel Statler

Presiding Officer

William J. Kerr, F.A.C.P., San Francisco, Calif.

a.m.

- 9:30 Plasma Proteins in Disease.
ROBERT F. LOEB, F.A.C.P., Professor of Medicine, Columbia University
College of Physicians and Surgeons, New York, N. Y.
- 10:30 The Clinical Implications of Sodium, Chloride and Potassium Metabolism.
GEORGE W. THORN, F.A.C.P., Associate Professor of Medicine, Johns Hop-
kins University School of Medicine, Baltimore, Md.
- 11:00 The Clinical Implications of Phosphorus and Calcium Metabolism.
DAVID P. BARR, F.A.C.P., Professor of Medicine, Washington University
School of Medicine, St. Louis, Mo.

Thursday Morning, April 24, 1941

Ballroom, Hotel Statler

Presiding Officer

Charles Hartwell Cocke, F.A.C.P., Asheville, N. C.

a.m.

- 9:30 The Autonomic Nervous System.
WALTER B. CANNON (by invitation), Professor of Physiology, Harvard
University Medical School, Cambridge, Mass.
- 10:30 The Hypothalamic Area.
PHILIP BARD (by invitation), Professor of Physiology, Johns Hopkins
University School of Medicine, Baltimore, Md.

Friday Morning, April 25, 1941

Ballroom, Hotel Statler

Presiding Officer

George Morris Piersol, F.A.C.P., Philadelphia, Pa.

a.m.

- 9:30 The Epidemiology and Immunological Factors in Hemolytic Streptococcus
Diseases.
FRANCIS G. BLAKE, F.A.C.P., Professor of Medicine, Yale University
School of Medicine, New Haven, Conn.
- 10:30 Progress in the Diagnosis of Certain Virus Diseases.
THOMAS FRANCIS, JR. (by invitation), Professor of Bacteriology, New
York University College of Medicine, New York, N. Y.

PANEL DISCUSSIONS

The Panel Discussions have been selected after careful consideration of topics which are of the greatest practical value to the physicians. Panel Discussers will gather from all parts of the country, and will be men who are not only highly qualified in their specialties, but who possess the capacity to discuss the specific questions clearly and concisely.

The Panel Discussions will be held from 12:00 m. to 1:15 p.m., daily, Tuesday through Friday at the Hotel Statler, except on Tuesday and Wednesday when one discussion will be held at the Hotel Copley Plaza.

The leaders will discuss special phases of the subject which have been assigned to them. Admission to the Panels will be by ticket. Application forms will accompany the formal program when later mailed to all members. When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. The discussers will answer those questions which seem to be most in demand.

CLINICS

Clinics will be held at each of the Boston hospitals during the mornings of the Annual Session. Each clinic will begin promptly at nine o'clock and the clinical morning will end with equal promptness at 11:30, in order to allow those who wish to attend the Panel Discussions to reach the meeting place on time.

The clinics will be true clinics. Each individual who holds one will himself give the history of the patients he presents, will demonstrate the essential physical findings, will establish his own diagnosis, and will outline the treatment and prognosis. In this manner it is hoped that the morning exercises will be truly practical and unmistakably clinical in nature.

For those interested in clinical-pathological correlation there will be one exercise each morning at the Harvard Medical School. This will be of two types: A Roentgen-Ray Conference at which roentgen-ray films will be demonstrated along with very short case histories, and the radiologist, faced with a film which he has never before seen, will establish his diagnosis, explaining his reasoning to the audience. His diagnosis will be confirmed or proved wrong by the pathologist.

There also will be more orthodox clinical-pathological conferences. A case report will be forwarded to each clinician who has been selected to lead a conference, and he will attempt to establish the diagnosis on his case from the data submitted to him. The diagnosis will be confirmed or proved wrong by the pathologist. Those interested in this form of exercise and wishing to have the case histories in their hands for study before the conferences are held may do so by notifying Dr. Reginald Fitz, Chairman, 319 Longwood Avenue, Boston.

PANEL DISCUSSIONS—12:00 M.—1:15 P.M.

Tuesday April 22	DISORDERS OF THE BLOOD *George R. Minot Charles A. Doan Claude E. Forkner Russell L. Haden	INTERPRETATION AND TREATMENT OF SYMPTOMS *John H. Musser Soma Weiss	BRIGHT'S DISEASE AND HYPERTENSION *Warfield T. Longcope A. M. Fishberg James P. O'Hare	NUTRITIONAL DEFICIENCIES *V. P. Sydenstricker Tom D. Spies Wm. B. Castle	PERIPHERAL VASCULAR DISEASE *Wallace M. Yater Richard B. Capps John Homans
Wednesday April 23	DISEASES OF THE CORONARY ARTERY *Robert L. Levy Samuel A. Levine Wm. D. Stroud	SULFANILAMIDE AND RELATED COMPOUNDS *Perrin H. Long Eli K. Marshall, Jr. Charles A. Janeway	EPILEPSY AND MIGRAINE *William G. Lennox Tracy J. Putnam	ESTIMATION OF SURGICAL RISK *Louis Hamman Frank H. Lahey	PNEUMONIA AND MENINGITIS *Francis G. Blake J. G. M. Bullowa Maxwell Finland
Thursday April 24	ALLERGY *Robert A. Cooke Francis M. Rackemann Richard A. Kern	ARTHRITIS *Walter Bauer W. Paul Holbrook Philip S. Hensch	ELECTROCARDIOGRAPHY *Arlie R. Barnes Paul D. White Frank N. Wilson	GASTRO-INTESTINAL PROBLEMS *Walter C. Alvarez Chester M. Jones	SYPHILIS AND ITS TREATMENT *Paul A. O'Leary Harold T. Hyman
Friday April 25	CONTAGIOUS DISEASES *Conrad C. Wesselhoeft John R. Paul Edwin H. Place	DOSAGES OF AND TOXIC REACTIONS TO DRUGS *Walter A. Bastedo Theodore G. Klumpp Harry Gold	PHYSIOLOGICAL ASPECTS OF HEART DISEASE *C. Sidney Burwell Carl J. Wiggers	ENDOCRINES *George W. Thorn Fuller Albright J. S. L. Browne	TUBERCULOSIS *J. Burns Amberson, Jr. Donald S. King Bruce H. Douglas

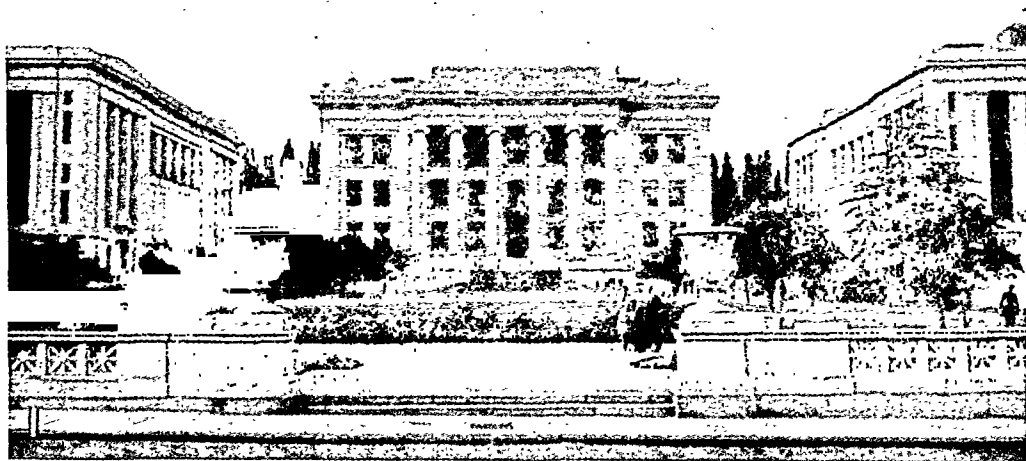
* Chairman.

BOSTON AS A MEDICAL CENTER

BOSTON may fittingly introduce herself to the American College of Physicians as a hostess whose medical activities have matured. This choice of expression does not arise as much from the storied reticence of the Back Bay as it does from the thought that in her colonial days Boston may have had opportunities for medical reflection which have ripened over the years into accepted and well developed practices. Thus we may trace her present literary proclivities back through the one hundred and thirteen years of the New England Journal of Medicine, through such earlier publications as those of Benjamin Waterhouse on vaccination, and the still earlier efforts of Zabdiel Boylston and Cotton Mather on inoculation, finally getting back to 1677, when the first medical publication in this country appeared under the delineating title: "*A Brief Rule, to guide the common people of New England How to Order Themselves and theirs in the Small Pocks, or Measels.*" This took the form of what used to be called a broadside, and was signed by "*a Friend, Reader to thy Welfare, Thomas Thacher.*" Dr. Thacher was a clergyman, but those who have taken over his concern for the health of the common people here wish to continue his solicitude toward his readers, and to express the hope that circumstances will permit many of our present readers to visit us in April.

Copies of the Brief Rule may be seen at the Boston Medical Library, together with other Colonial papers, such as Governor Winthrop's receipt book in which the prescriptions for emetics don't need to be concocted and swallowed, but merely read, to be effective. The buildings of the Boston Medical Library harbor 185,000 volumes, contain reading, study and assembly rooms, the offices of the Massachusetts Medical Society, and the editorial rooms of the New England Journal of Medicine and of the Journal of Bone and Joint Surgery. Sprinkled through the City and its suburbs there are larger staffs, more eminent individuals, and grander piles of masonry by far, but the common medical touch has nowhere been more carefully retained than in the services and uses to which these organizations devote themselves at "8 The Fenway."

The approval of the Council on Medical Education of the American Medical Association is given to three medical schools in Boston: those of Boston University, of Harvard University and of Tufts College. Altogether these three schools graduate about two hundred and seventy-five physicians each year. They are the medical components of a much vaster educational output, which includes the graduates of such well known institutions as Boston College, Boston University, Emmanuel College, Harvard University, Massachusetts Institute of Technology, Radcliffe College, Regis College, Simmons College, Tufts College and Wellesley College. More than 18 per cent of the diplomates of the National Board of Medical Examiners received



GROUP I. (BOSTON MEDICAL SCHOOLS.)

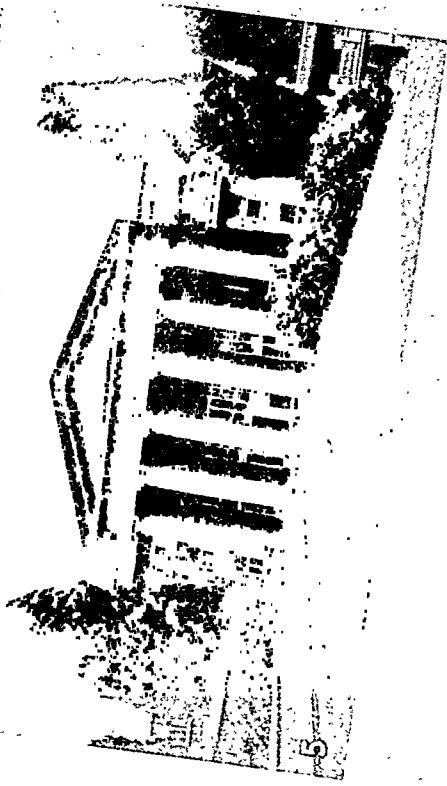
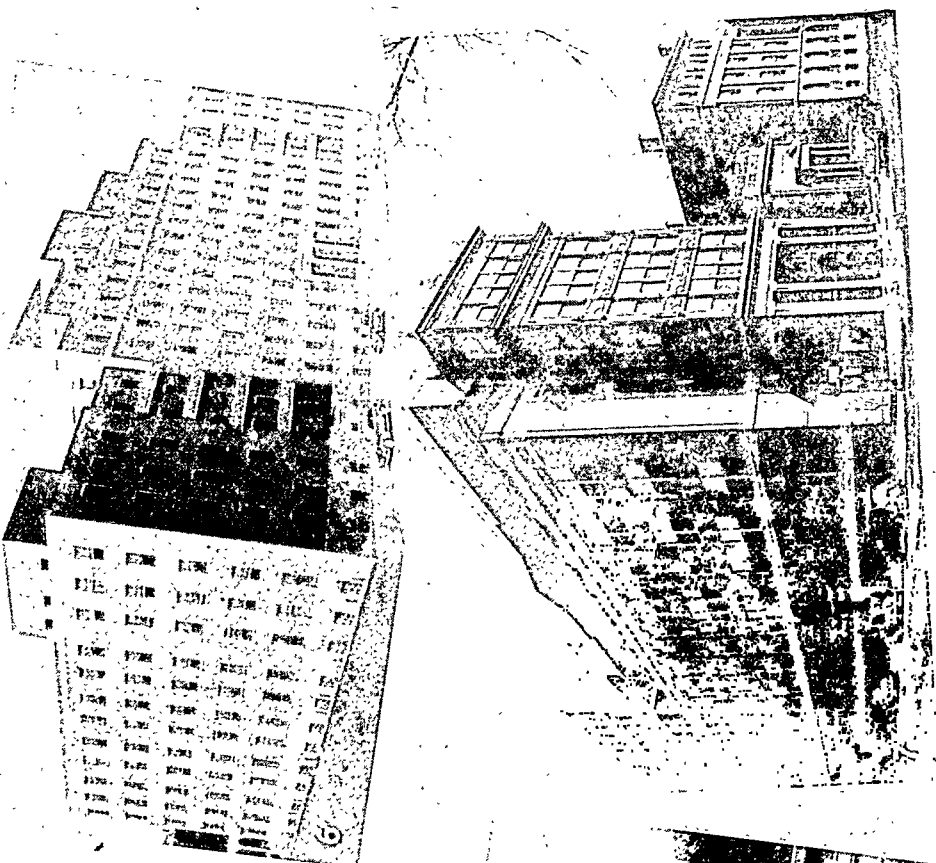
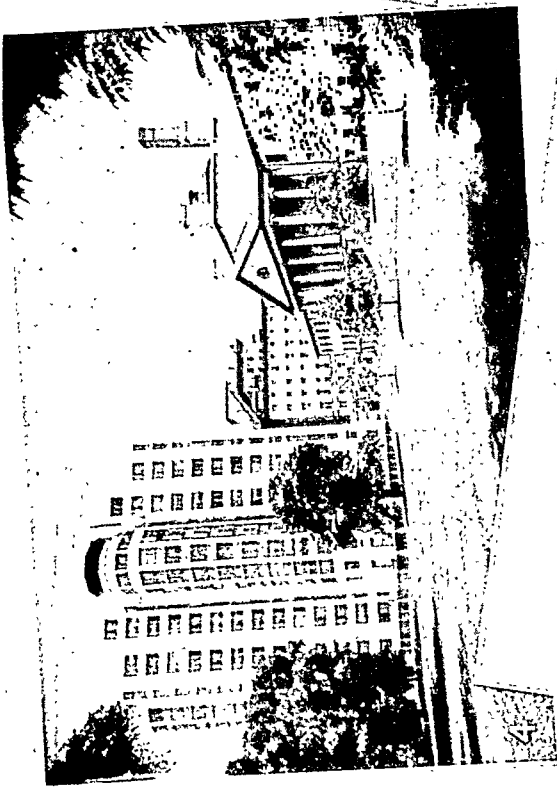
1. Harvard Medical School.
2. Tufts College Medical School.
3. Boston University School of Medicine.

their medical education in Boston. The three medical schools coöperate in many ways. For example, Harvard's Department of Legal Medicine, the only full time department devoting itself to this subject in the country, makes its courses available to the students of all three schools, and instruction is participated in by members of the several faculties.

The first public health regulation on the North American continent was made in 1647 when "*all our own or othr vessels comeg from any pts of ye West Indies to Boston harbor shall stop and come to an anchor before they come at ye Castle, undr ye poenalty of 100£, and that no pson comeing in any vessell from the West Indies shall go a shore in any towne, village, or farme, or come within foure rods of any othr prson,*" etc. In 1849 the General Court of Massachusetts authorized a commission to prepare a sanitary survey of the State, the result of which was the famous Lemuel Shattuck report of 1850. This report recommended the creation of a State Department of Public Health, which was established a few years later. Without counting milestones or recounting priorities, it is fair to say that Massachusetts has always had an active and progressive administration of public health. Focused as it is at the State House in Boston, this administration has often been an integral part of the educational side of public health. The Harvard School of Public Health, as well as Departments of Health or Preventive Medicine, or Hygiene, or Sanitation in other institutions have all provided a generous educational opportunity in this field. In recent years there has been developing a correlation between these various departments which tends to place the facilities of all at the disposal of each. A senior student in any of the approved medical schools in Boston, for example, may arrange to spend his time at the Harvard School of Public Health, provided he gives evidence of his particular interest and qualification in this direction.

The administration of public health in the City of Boston has been expanded in the past decade by the establishment of district health units, housed in buildings built by the White Fund, and operated by the City. The result has been a decentralization of activities which has facilitated the organization of preventive and welfare clinics. This has provided another opportunity for medical school affiliation, as well as the more effective accomplishment of public health functions, and these health units are now utilized for instruction in both the graduate and undergraduate departments of the medical schools.

The scope of opportunity for graduate medical study in Boston may best be indicated by listing the available institutions and their facilities. These are mentioned as in the last lists approved by the Council on Medical Education and Hospitals of the American Medical Association. Inaccuracies in the compilation, if present, may be due to the fact that revision is continually taking place. Many readers will be able to season this list with reminiscences



GROUP II. (BOSTON HOSPITALS.)

(Approved by the American Medical Association for Residencies and Internships.)

4. Massachusetts General Hospital. 5. Peter Bent Brigham Hospital.
6. U. S. Marine Hospital. 7. Massachusetts Memorial Hospital.

of their own hospital days, and will be able to see evidence of the continual expansion that has been taking place.

BETH ISRAEL HOSPITAL: Internships. Residencies or Fellowships in Medicine, Otolaryngology, Radiology, Surgery and Urology.

BOSTON CITY HOSPITAL: Internships. Residencies or Fellowships in Anesthesia, Communicable Diseases, Dermatology and Syphilology, Medicine, Neurology, Neurosurgery, Obstetrics and Gynecology, Ophthalmology and Otolaryngology, Orthopedic Surgery, Pathology, Pediatrics, Radiology, Surgery, Thoracic Surgery, Tuberculosis and Urology.

BOSTON FLOATING HOSPITAL: Residencies in Pediatrics.

BOSTON LYING-IN HOSPITAL: Residencies in Obstetrics and Pathology.

CARNEY HOSPITAL: Internships. Residencies in Obstetrics and Gynecology.

CHILDREN'S HOSPITAL: Residencies and Fellowships in Orthopedic Surgery, Pathology, Pediatrics, Radiology and Surgery.

COLLIS P. HUNTINGTON MEMORIAL HOSPITAL: Residency and Fellowships in Malignant Disease.

FAULKNER HOSPITAL: Internships.

FREE HOSPITAL FOR WOMEN: Residencies in Gynecology.

HOUSE OF THE GOOD SAMARITAN: Residency in Cardiology.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL: Residencies in Medicine.

LAHEY CLINIC: Residencies and Fellowships in Anesthesia, Medicine, Neurosurgery, Otolaryngology, Orthopedic Surgery, Radiology, Surgery and Urology.

MASSACHUSETTS EYE AND EAR INFIRMARY: Residencies in Ophthalmology and Otolaryngology.

MASSACHUSETTS GENERAL HOSPITAL: Internships. Residencies and Fellowships in Anesthesia, Dermatology and Syphilology, Medicine, Neurology, Neurosurgery, Orthopedic Surgery, Pathology, Pediatrics, Psychiatry, Radiology, Surgery and Urology.

MASSACHUSETTS MEMORIAL HOSPITALS: Internships. Residencies and Fellowships in Anesthesia, Medicine, Obstetrics, Pathology, Radiology, Surgery and Urology.

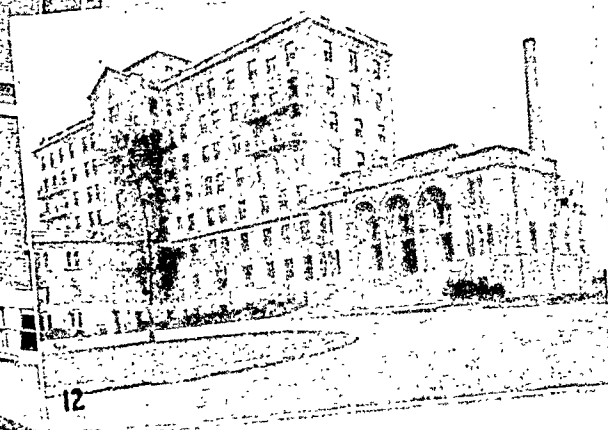
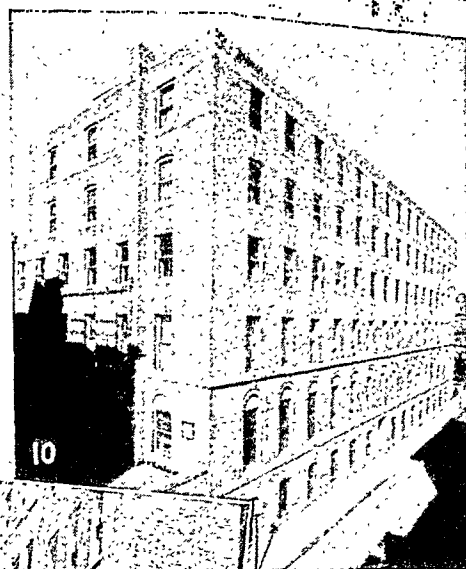
NEW ENGLAND DEACONESS HOSPITAL: Residencies in Malignant Disease, Pathology and Radiology.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN: Internships.

PETER BENT BRIGHAM HOSPITAL: Internships. Residencies in Medicine, Pathology, Radiology and Surgery.

ST. ELIZABETH'S HOSPITAL: Internships.

Outside of what is colloquially known as "Boston Proper" (for which in the above list Brookline was included and Long Island omitted), there are many other approved internship and residency opportunities, such as those at the Long Island Hospital, Chelsea Memorial Hospital, U. S. Naval Hospital, Lynn Hospital, Salem Hospital, Beverly Hospital, Cambridge Hospital, Cambridge City Hospital, Malden Hospital, Waltham Hospital, Newton Hospital, Quincy City Hospital and others. These rightfully belong in any catalogue of Medicine in Greater Boston, as do also the McLean Hospital and several of the State Institutions for the Insane, most of which provide approved residencies in psychiatry. The newly opened United States Marine Hospital is also a part of our medical life. Its opportunities for graduate education are not listed by the American Medical Association nor are those



GROUP II—Continued

8. Boston City Hospital.
9. Carney Hospital.

10. Boston Dispensary.
11. Joseph H. Pratt Diagnostic Hospital.
12. Beth Israel Hospital.

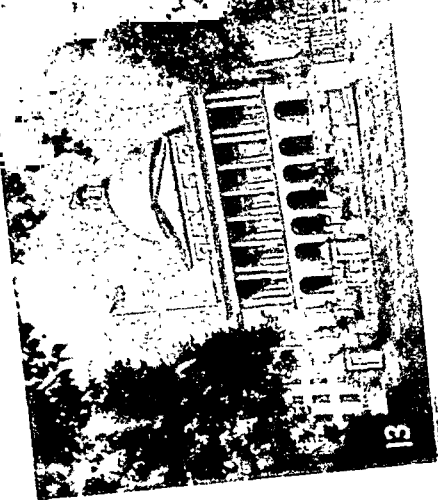
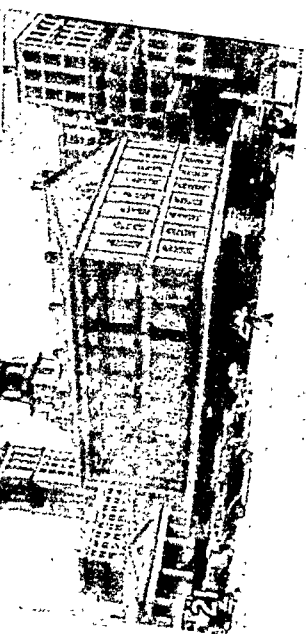
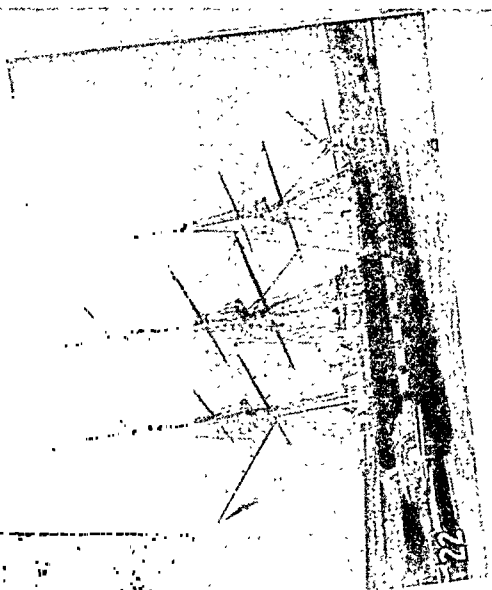
of several other local institutions such as the House of the Good Samaritan. Likewise 12 full time fellowships in Domiciliary Medicine at the Boston Dispensary are not listed by the American Medical Association because that is a category with which it has not as yet concerned itself. None of those professing interest in what they call "socialized medicine" in recent years has made a study of this Boston service, yet it makes over fifty thousand sick calls a year to the poor of the City! The Boston Sanitarium at Mattapan and the Middlesex Sanitarium at Waltham are available for the study of tuberculosis.

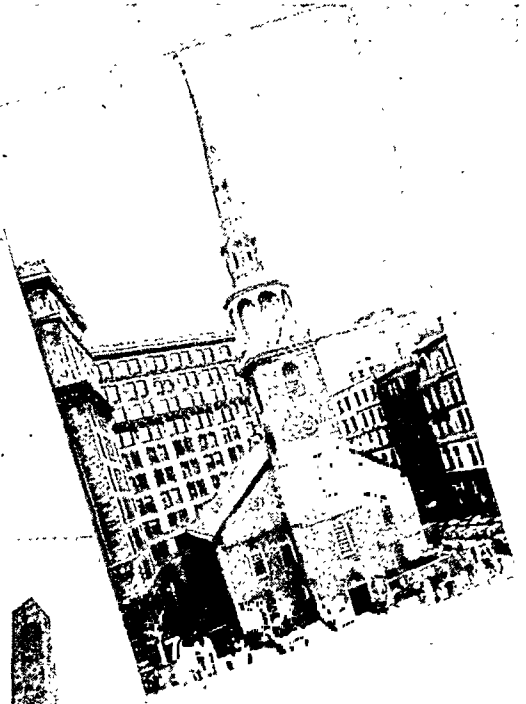
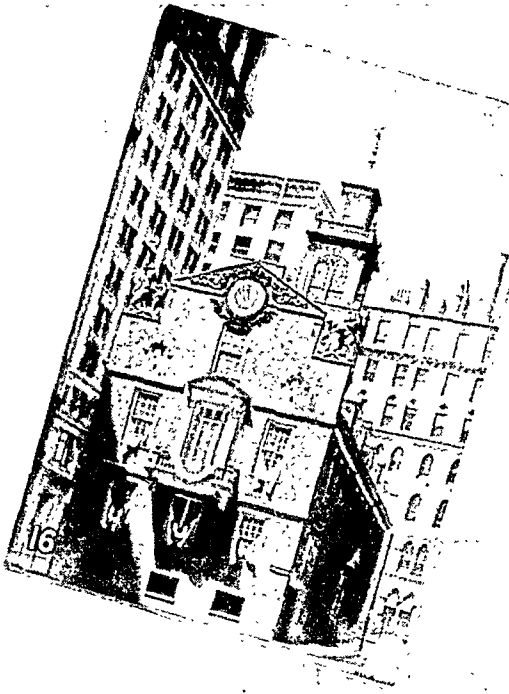
Very large outpatient clinics are of course available. One of them alone has thirty-one clinical divisions and received 171,000 visits from 26,000 people in the last calendar year. Two others are of similar proportion, and many of them are widely used for educational purposes.

In the recently promoted field of postgraduate education, for physicians already established in practice, Boston is the center for three separate and somewhat distinctive efforts. I. Harvard Medical School offers a large number of Courses for Graduates on a tuition fee basis. These courses place the facilities of the medical school in most of the basic science and clinical departments at the disposal of the profession. There is at the present time an increasing demand for such of these courses as are acceptable to the various certifying boards. II. The Massachusetts Medical Society sponsors a peripatetic program, supported largely by Federal funds, and designed to bring instruction to the doctor without asking him to leave his practice for more than a few hours at a time. The Medical Society has also jointly sponsored three postgraduate assemblies of the usual type, in which large groups are addressed by lecturers who have been carefully selected in advance. III. The third effort is that of the postgraduate division of Tufts Medical School, made possible by grants from the Bingham Associates Fund, the primary objective of which is improvement of the practice of medicine in the State of Maine. This arrangement also provides courses for technicians, dietitians and the other ancillary workers in the care of the sick. Physicians may choose between, or combine, intensive courses in the city and the peripatetic courses near home, the one variety often being designed

GROUP III. (BOSTON'S HISTORIC VIEWS.)

13. Massachusetts State House.
14. Paul Revere House—Oldest house in Boston, built about 1660 and occupied by Paul Revere until 1800.
15. Skyline of Boston with Public Garden and Boston Common.
21. Faneuil Hall—Cradle of American Liberty because of meetings held here prior to Revolution; first presented to Boston in 1742 by Peter Faneuil for a market place and public town hall.
22. U. S. Frigate Constitution—permanently moored at Navy Yard in Charlestown; familiarly known as "Old Ironsides"; launched, 1797; was in forty engagements and never suffered defeat; restored by funds donated by school children of America.





to complement the other. These courses are correlated at the New England Medical Center, which is the name given to an integration of the Boston Dispensary, the Floating Hospital, the Pratt Diagnostic Hospital and Tufts Medical School.

Shrines and relics of colonial life abound in Boston and the surrounding countryside, and many of our visitors will wish to visit them. The earliest building is the Fairbanks House, 1636, in Dedham. This is among the most picturesque houses in America. One of the most accurate restorations of a seventeenth century structure is that of the Old Brown House, 1663, in Watertown, while those interested in the earliest brickwork will want to see the Peter Tufts, often called the Cradock House, in Medford. Among the eighteenth century buildings is the Wayside Inn at Sudbury. In Boston itself are the Old State House, Faneuil Hall, the Old South Meeting House, the Paul Revere House and many other points of interest. Space does not permit their being mentioned here in anything more than a fragmentary list.

Boston is one of the most attractive shopping centers in the country. Its port facilities include modern piers and docks with direct highway and railroad connections and eight miles of thirty to forty foot berthing space. At the present time the port is especially busy because of the large number of manufacturing plants in New England that are engaged in completing defense assignments, for which Boston is the natural marine outlet. Those who enjoy sea voyages may wish to travel to and from the convention by the several passenger coastwise services that are available.

However our guests may elect to travel, and wherever they may elect to stay, in private homes, hotels or clubs, we wish to extend to each of them a cordial and hearty welcome. (With Thomas Thacher, we shall consider it our privilege to be "*A Friend, Reader to thy Welfare.*")

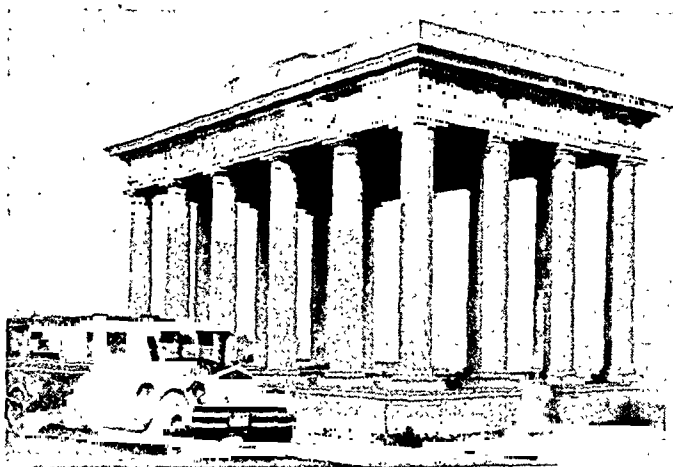
GROUP III—Continued

16. Old State House—here met colonial courts and legislators, the town and city governments and the General Court of the Commonwealth; John Hancock was here inaugurated first Governor of Massachusetts in 1780; in front of it occurred the burning of stamp clearances and the Boston Massacre; here were the whipping post and the stocks; contains large collection of relics.
17. Old South Meeting House—built 1729; protest meetings held here against forcing citizens into the English Navy, also to decide the fate of the hated tea tax; used by the British as a riding school during the siege of Boston; restored and used as church until 1872.
18. Bunker Hill Monument—221 feet high, on Breed's Hill within the lines of the American redoubt, center of the Battle of Bunker Hill; June 17, 1775; General Lafayette assisted at laying of corner stone, June 17, 1825.
19. Fishermen's Memorial, Gloucester—memorial to Gloucester fishermen who have lost their lives at sea.
20. Concord Bridge—"By the Rude Bridge that Arched the Flood
Their Flag to April's Breeze Unfurled
Here Once the Embattled Farmers Stood
And Fired the Shot Heard Round the World."

POST CONVENTION TOUR TO PLYMOUTH, THE PILGRIM SHORE, AND CAPE COD

THE Annual Session in Boston affords an opportunity to offer to members and friends of the College an organized, all-expense tour of historic Plymouth, the Pilgrim Shore and Cape Cod. Doctors especially are reputed to like history. This will be a tour of the cradle of history in the United States. Not only is the Cape tied up with the Pilgrims and the early settlers, but along its shores Gosnold and other discoverers sailed.

The party will leave the Hotel Statler, Boston, at 5:30 p.m., Friday, April 25 by private de luxe motor coaches and reach Plymouth, Hotel Plymouth Rock, for dinner and the night. In the morning of the 26th, Pilgrim Hall, Forefather's Monument, Burial Hill and Plymouth Rock will be visited, and after a tour of the town, the party will proceed through Sandwich, where the



Canopy over Plymouth Rock.

famous glass was made, Barnstable, Yarmouth, Dennis, Brewster and Orleans, with lunch in Provincetown. Returning in the afternoon by the South Shore, the party will pass through Chatham, Hyannis, Falmouth, glimpsing the islands of Nantucket and Martha's Vineyard, motoring along Buzzard's Bay, to return to the hotel at Plymouth for dinner and the night. On the morning of the 27th the party will visit the John Alden House, the Home and Tomb of Daniel Webster, the Old Oaken Bucket House, the Old Stone Church, the tomb of Presidents, and the Adams Mansion in Quincy, reaching Boston in time for convenient departures by trains to all points by noon.

But let our conductor, Mr. Leon V. Arnold, describe the tour—

“Probably more has been written about Plymouth, the Pilgrim Shore, and Cape Cod than any other section of the United States. Historical novels

have been numerous and fiction using its architecture, customs, and salt speech as a back-drop have always been popular.

"At five-thirty in the afternoon our private motor coach leaves the Statler Hotel taking the direct route to Plymouth where we shall have dinner and spend the night. Our hotel is located on a bluff directly overlooking the historic Plymouth Rock.

"The next morning we shall make a tour of Plymouth and see many of the reminders of the vigorous and purposeful past, Pilgrim Hall, Forefather's Monument, Burial Hill, The Howland House, 1666, the Sparrow House, 1640, William Harlow House, 1677, and many other places connected with the early settlement.

"After our tour of Plymouth we make the complete circuit of Cape Cod. The Cape is rich in dignity and quaintness. Beautiful Georgian houses drowse beneath fine old elms. The air is heavy with the smell of salt and pine. Life is not rush and bustle. Cape Cod was settled by the Pilgrims almost as early as Plymouth. It is the Old Colony.



Pilgrim Hall, Plymouth.

"Soon after entering the Cape through Sagamore we reach Sandwich which was settled in 1637. Its bounds of land were laid out by Miles Standish and John Alden who were sent as commissioners from Plymouth. Sandwich is one of those dream towns seldom realized, an early New England village so old and so perfect that you forget the modern world as you drive slowly through the great nave of spreading elms that edge the streets. Joseph Jefferson said, 'It is the handsomest town out of England.' Here, too, was the site of the famous glass factory of more than a half century ago.

"Barnstable is another old Pilgrim town. The hilly streets are shady with magnificent trees and lined with fine old houses, each a real museum piece, but delightfully liveable, between which you catch glimpses of the blue water of the harbor. James Otis, the fiery orator, was born here.

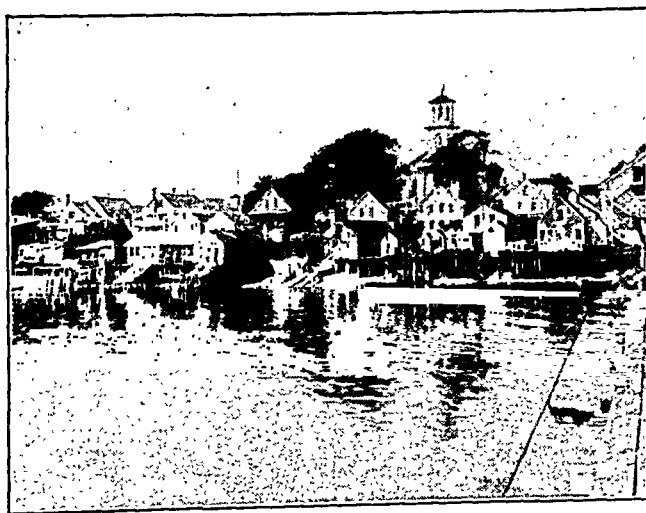
"Yarmouth is a one street town—but such a street—where house after house remains as it was built in the 18th century and now highly prized by

its 20th century owners. Yarmouth may be called one of the prettiest towns in the world.

"Dennis was named after its first minister who was noted for the 'mirthfulness of his disposition.' Here most of the houses are small, old,



The Elms in Old Sandwich.



Provincetown.

gray shingled and stand alone in their big yards. Adjoining are bayberry pastures, wooded hills, and great salt marshes. It is and always has been the center of a farming community.

"Brewster, a good old Pilgrim name, looks much like itself a century and a half ago.

"Orleans has had a long history crammed with exciting incidents. Near here Lief Ericsson is believed to have landed.

"The fields around Eastham were so fertile that they tempted almost half of the Plymouth colony to emigrate there in 1646. There was wealth in the sea, too, for Thoreau writes, 'In 1662 the town agreed that part of every whale cast ashore should be appropriated for the ministry.'

"Wellfleet still holds the flavor of its fishing days. In the years preceding the Revolution nearly every man and boy was a whaler. Scarcely an old family now remains that does not cherish a whaling log of some ancestor.



Pilgrim Monument, Provincetown.

"We pass through North Truro with its three churches 'set on a hill to be nearer God and a landmark for fishermen' and soon reach Provincetown on the tip of the Cape.

"Provincetown is first and always a fishing village. It was here that the Mayflower first dropped anchor and here the Compact was signed. This was the first state paper in America, a simple, democratic self-imposed charter of principles that 150 years later fired the spirit and provided the will to do in the American Revolution.

"In the town the shore crowds the houses, the houses crowd the streets, and during the summer season the artists with their easels crowd everything. Commercial Street is only twenty feet wide including the sidewalk. Back

of the town are the dunes, the Desert of Provincetown, which we shall see from the top of the Pilgrim Monument.

"We shall lunch in Provincetown. The return route will be detailed in the next issue of the ANNALS.

"You have always wanted to see this historic section. You will enjoy seeing Spring in New England. It is economy of both time and money to see them now. Members as far west as Chicago can be in their offices on Monday morning."

Mr. Arnold will accompany the party. Many of the members will remember him very pleasantly in connection with the Bermuda Cruise, the New Orleans meeting, and the Post Convention trip to Mexico City.

Early reservation is necessary for the accommodation is limited. Send in your reservation now to Leon V. Arnold, 36 Washington Square West, New York City. Final payment will not be due until April 10 and even then your deposit will be returned if for any reason you must change your plans. Every necessary expense, \$27.75 per person.

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THE CLINICAL MANIFESTATIONS OF NICOTINIC ACID AND RIBOFLAVIN DEFICIENCY (PELLAGRA) *

By V. P. SYDENSTRICKER, M.D., F.A.C.P., *Augusta, Georgia*

THE genesis of spontaneous deficiency disease in human beings is such that it is quite unlikely that an uncomplicated avitaminosis should occur. This is particularly the case in deficiencies of the B group of vitamins. These substances commonly occur together in their natural sources and have closely related functions in essential metabolic processes so that any circumstance which causes inadequate intake, poor utilization or rapid depletion of one of these vitamins is almost certain to affect the whole group. The title of my lecture suggests that pellagra is a combination of nicotinic acid deficiency and ariboflavinosis. This is only partly true, evidences of thiamin deficiency are seldom absent and, as knowledge increases, it is likely that evidences of other avitaminoses may be recognized.

The term pellagra implies the presence of symmetrical, definitely localized dermatitis which in our present state of knowledge is considered a specific manifestation of nicotinic acid deficiency. It is conservative to think of pellagra as a B group avitaminosis in which lack of nicotinic acid is predominant but in which other vitamins are depleted to a level of physiologic inadequacy. Since many persons with B group deficiencies fail to develop dermatitis it seems necessary to abandon the term "pellagrous" for those manifestations of the syndrome not characterized by typical skin lesions and to refer to them in terms of the specific avitaminosis shown to be concerned.

Recognition of the symptoms and signs of predominant avitaminoses has become possible only since adequate supplies of pure synthetic vitamins have been available for differential clinical tests. Coincidentally it has been possible to correlate the probable chemical activities of the vitamins with their physiologic functions in health and to link the manifestations of deficiency diseases with perversion of these functions. When Elvehjem and his asso-

* A clinical lecture presented at the Cleveland meeting of the American College of Physicians, April 4, 1940.

From the Department of Internal Medicine, University of Georgia School of Medicine and the University Hospital, Augusta, Georgia.

ciates¹ demonstrated the importance of nicotinic acid in nutrition and Sebrell and Butler^{2,3} discovered the signs of riboflavin deficiency in human subjects, it was immediately suspected that the clinical significance of these observations depended on the participation of nicotinic acid and riboflavin in various metabolic processes already well known to physiologists and biochemists.

The derivation of energy from carbohydrate foods and certain respiratory processes of cells depend on the chemical activity of compounds of the B group of vitamins with phosphoric and adenylic acids. The utilization of carbohydrate is a matter of fractional dehydrogenation, which is the chemical equivalent of oxidation, followed by decarboxylation. Nicotinic acid is the chemically active fraction of the coenzymes diphosphopyridine nucleotide (coenzyme I) and triphosphopyridine nucleotide (coenzyme II) which are essential to the intermediate metabolism of glucose. Thiamin is the reactive portion of cocarboxylase (diphosphothiamin). Riboflavin is, similarly, the active residue of the "coferment" of Warburg, which is ubiquitous in cells and concerned with many enzyme reactions; also it is thought to function as an intracellular respiratory ferment in the absence of haem.

Triphosphopyridine nucleotide is active in the oxidation of hexose monophosphate. The aldehyde group of the sugar is oxidized, with reduction of the pyridine nucleotide. A specific protein from red blood cells (or yeast) which unites both with hexose monophosphate and triphosphopyridine nucleotide must be present. The reduced nucleotide is oxidized by flavoprotein and so regenerated, flavoprotein in turn is oxidized by molecular oxygen. Diphosphopyridine nucleotide functions in the utilization of hexose diphosphate. After the cleavage of hexose diphosphate into two molecules of triose phosphate, diphosphopyridine nucleotide dehydrogenates (oxidizes) triose, losing oxygen which is restored by flavoprotein, the reduced flavoprotein is in turn reoxidized by molecular oxygen, possibly from haem. The phosphoglyceric acid resulting from the dehydrogenation of triose undergoes a series of enzymatic reactions with the production of phosphopyruvic acid. This, in the presence of adenylic acid is decomposed into pyruvic acid. Pyruvic acid may be broken down by two systems. By the combined action of diphosphothiamin (cocarboxylase) and the flavoprotein-cytochrome chain, it is oxidized to CO_2 and H_2O . In the absence of molecular oxygen, pyruvic acid yields oxygen to reduced diphosphopyridine nucleotide, being converted into lactic acid, while the pyridine nucleotide is regenerated.

Thiamin, nicotinic acid and riboflavin are thus concerned with the continuous processes of cellular nutrition and respiration and while they function in part as activators which are continually regenerated, they also are components of coenzymes which are used up and require constant replacement. All three vitamins are probably normally present in all cells. The symptoms and signs of avitaminosis may be regarded as results of chemical disturbances of cellular function due to failure of coenzyme action. The clinical phe-

nomena depend on the grade of vitamin depletion and the rapidity with which it is brought about.

The factors which contribute to the production of clinical manifestations of vitamin deficiency are many and often their influence seems obscure or even paradoxical. The fundamental mechanism is the effort of the body to derive energy from carbohydrates in excess of the available supply of vitamins. The physiologic processes are normal in so far as intrinsic cellular metabolism is concerned; disease results from failure of the extrinsic supply of substances necessary to replenish the coenzymes. Inadequate diet is the common cause of endemic avitaminoses though many other factors are active. The nature of an inadequate diet is still widely misunderstood and starvation is constantly confused with bad nutrition. An inadequate diet may be, in fact usually is, of high caloric value because of its high carbohydrate and fat content. Bleached wheat flour, highly milled cornmeal, glucose syrup, lard and fat pork are the main constituents of such a diet. The use of soda or baking powder instead of yeast to leaven bread made of flour or cornmeal and the substitution of hominy grits for potatoes are contributing factors. The dietary vagaries of individuals who for various reasons abstain from the common protective foods are a common and frequently overlooked source of nutritional disease. The use of an inadequate diet seldom or never produces complete or acute avitaminosis since no naturally selected diet is apt to be completely lacking in any single vitamin. In the course of time, however, chronic partial deficiency produces functional and organic changes which interfere with the absorption or utilization of the small amounts of vitamins available so that finally, a critical level of depletion is reached.

In individuals whose nutritional balance is chronically poor but still adequate at a given level of metabolism, any factor which creates an increased demand for the utilization of energy may precipitate the clinical manifestations of avitaminosis by causing the rapid depletion of coenzymes. The common conditions encountered clinically are unaccustomed work, fever, pregnancy, and hyperthyroidism, the substitution of alcohol for food and therapeutic maintenance on parenterally administered glucose. The derivation of energy from alcohol involves the same coenzyme functions that are active in the metabolism of glucose and when the daily intake of alcohol is sufficient to satisfy a major portion of the caloric requirement, depletion of vitamins is rapid and often clinically complete. It is not generally recognized that "intravenous feeding" with dextrose solutions produces a similar depletion and that many of the severe complications of this frequently necessary procedure are due to avitaminosis. Occasionally when patients with diabetes poorly controlled by relatively low carbohydrate diet and small amounts of insulin are changed to a high carbohydrate regimen with the requisite increase in insulin, acute avitaminosis results, evidently from the greatly increased derivation of energy from glucose.⁴

Loss of ingested vitamins from vomiting or diarrhea is equally as important as severely reduced intake in producing or prolonging avitaminosis. Less obvious causes of deficiency which may attain a serious grade are failure of absorption or utilization of vitamins when adequate amounts are ingested. Gastric achlorhydria seems to be particularly potent in preventing the extraction of vitamins from their natural sources in food. It is well known that achlorhydria is common in all the deficiency diseases. In pellagra it is more frequent than in any of the other syndromes and there is reason to think that atrophy of the gastric mucosa with failure of the acid secreting function is a specific effect of nicotinic acid deficiency. The administration of nicotinic acid frequently results in the reappearance of acid⁵ though as long as two years of constant treatment may be necessary to produce this effect.⁶ In fatal pellagra the mucosa of the entire gastrointestinal tract is atrophic and while no direct proof can be offered, it seems quite likely that this is a result of prolonged partial deficiency of the B vitamins as well as a contributing factor to the failure of absorption or utilization of the vitamins ingested. It has been shown that the phosphorylation of riboflavin occurs in the mucosa of the small bowel⁷ so that atrophy or dysfunction of the mucosa of this part of the intestine may be of equal importance with similar changes in the stomach. Edema of the intestine also interferes with absorption of vitamins and probably contributes to the deficiencies so frequently seen in heart disease, nephritis, cirrhosis of the liver and obstruction of the mesenteric circulation from any cause. It seems probable that edema due to thiamin deficiency may have a similar effect though there are no valid observations. The high incidence of avitaminoses in patients with arteriosclerosis suggests that this condition may contribute to their production. There seem to be at least three possible mechanisms. Diminished capillary circulation resulting from narrowing of arteries and arterioles may interfere with absorption of vitamins from the gastrointestinal tract or it may reduce the amount reaching the peripheral capillary beds of all tissues. The third possibility is loss of these rapidly eliminated vitamins due to the nocturnal diuresis so common in arteriosclerotic disease of the kidneys. In a considerable number of instances of pellagra there seems to be no question of an adequate vitamin intake and no demonstrable failure of absorption; the only logical explanation in such cases would seem to be failure of utilization. Little is known of the factors which condition utilization. It is possible that any disease or serious dysfunction of the liver may interfere with the phosphorylation or storage of thiamin and nicotinic acid or with the storage of riboflavin phosphate. It is also possible that there is definite interrelation of the functions of the B group of vitamins so that marked deficiency of one may prevent the normal activity of the others.

Though much effort has been expended in attempts to find rapid and relatively simple tests for the detection of subclinical grades of deficiency of the B vitamins, no methods are as yet available. It is possible to estimate the concentration of thiamin and nicotinic acid in the blood and of riboflavin

in the urine and it is certain that known methods will be sufficiently simplified to make them useful for diagnosis. For the present the recognition of the pellagrous syndrome depends on familiarity with its various manifestations and the application of therapeutic tests under controlled conditions. It has been possible to identify the symptoms and signs resulting from deficiency of thiamin, nicotinic acid and riboflavin by maintaining patients on a diet extremely poor in all vitamins but supplemented with all but the one under investigation. Once the clinical picture of a relatively pure avitaminosis is determined by this method, the validity of the experiment can be proved by the administration of a single vitamin to patients presenting a specific symptom complex.

Only recently has it been recognized that there is much difference between the clinical manifestations of severe acute and chronic partial deprivation of a vitamin. The evidences of acute avitaminosis are largely functional because the deficiency is produced too rapidly for important tissue changes to occur. In chronic partial deficiencies, functional disturbances occur early, are mild at first but progressively become more severe and finally characteristic anatomical changes are produced. Clinically, all grades of mingling of acute and chronic effects of avitaminosis are seen. Because neurons are more sensitive to disturbances of nutrition and oxygen supply than other cells, signs and symptoms referable to the nervous system are particularly common.

In the chronic partial deficiency of B vitamins which finally results in the syndrome of pellagra, the symptoms and signs of nicotinic acid deprivation are prominent. Mild psychic disorders may precede other manifestations by weeks or months.^{6, 8} Neurasthenic complaints of all sorts are common. Slight mental retardation, loss of memory for recent events, apprehension, confabulation, depression or mild delusional states may recur for months or years. Partial deafness, particularly for high pitched tones, may be the presenting symptom.⁹ Digestive disturbances, particularly gastric discomfort after meals, burning of the esophagus and stomach, flatulence and constipation are almost invariable, anorexia is very apt to develop, with decreased intake of all sorts of food. Soreness of the tongue, often with no visible glossitis, is a common complaint. In women there is apt to be a concurrent non-specific vaginitis, usually with hyperesthesia and dyspareunia. It is characteristic that such symptoms undergo spontaneous remission and recurrence. Recurrence or relapse is apt to be seasonal, appearing in spring and fall, though it may follow infection, unaccustomed physical exertion or trauma of any sort. As time goes on, food intake is apt to be reduced in the effort to mitigate indigestion or as a result of anorexia. With increasing malnutrition glossitis proceeds to atrophy of the lingual papillae and functional or anatomic changes in the gastric mucosa result in achlorhydria. It is likely that atrophic changes in the intestinal mucosa keep pace with those in the stomach. Diarrhea may be initiated by the presence in the bowel of large amounts of undigested food, by failure of

absorption of fluids by an atrophic mucosa or by the development of an infectious or ulcerative colitis. Progressive mental deterioration is apt to further limit the intake of food. Infection, particularly with Vincent's organisms or moniliae, is apt to occur in the mouth or esophagus, probably from failure of normal defense mechanisms. Finally, with extreme depletion of vitamins resulting from the combination of poor intake, poor absorption and inadequate utilization, such serious cerebral manifestations as hebétude, delirium, dementia or stupor or even the encephalopathic state ensue. At any stage in the progress of psychic and gastrointestinal symptoms patients may complain of paresthesias, particularly general formication, localized sensations of heat or burning and tingling of the palms and soles. Neuritic pain is frequent and may be associated with muscular weakness and depressed reflexes. In rare instances the picture of subacute combined sclerosis is seen. Photophobia, burning and itching of the eyes and dimness of vision are not uncommon.

Dermatitis is an essential part of the picture of pellagra and may occur at any stage. Various skin lesions are characteristic. There may be only symmetrical erythema of the dorsal surfaces of the hands or erythema may occur around the neck, over the upper sternum, the malar eminences and forehead. Frequently it is found on the elbows, forearms and feet. Rather commonly a vesicular or bullous dermatitis is superimposed on erythema. The genitalia, perineum and knees may be sites of dermatitis similar to that on the exposed surfaces; at times balanitis or vaginitis may be severe. In rare instances there is rapid necrosis of the skin over the dorsal surfaces of the hands, elbows, knees and feet; in such cases decubitus ulcers are apt to develop acutely. Dermatitis of the typical symmetrical distribution on the extremities often seems to follow trauma of any sort such as exposure to sunlight, radiant heat, friction or chemical irritants. It seems likely that perineal and genital lesions result from the irritation produced by decomposing urine and sebaceous secretions. The complete picture of pellagrous dermatitis has been seen to develop following intensive radiation of the mediastinum. It seems possible that dermatitis is always a result of some form of trauma to the skin in the presence of avitaminosis or that skin areas already "traumatized" may react with the production of dermatitis when a severe grade of avitaminosis is rapidly produced. Instead of the symmetrical erythematous and vesicular types of dermatitis, there may be simply thickening and pigmentation of the skin over the usual areas. Quite often there is localized follicular keratosis of the sebaceous glands of the forehead, nose, malar eminences and chin producing the "shark skin" eruption long associated with pellagra. Less often dermatitis is seborrheic and localized over the ears, malar eminences, *alae nasi* and chin. Not infrequently the lips are painful, red and desquamating with fissures at the commissures.

There are as yet no laboratory aids which are generally available for the diagnosis of avitaminoses of the B group. Much effort has been expended

on methods for quantitative determination of vitamins and coenzymes in the blood and urine and it is likely that simplified procedures will be developed which will be generally useful. At the present time such determinations are too complicated and time consuming to be of clinical importance. It seems likely that urinary excretion tests will be more helpful than determinations of the concentration of vitamins in the blood since the tissues seem to retain the vitamins until a really critical stage of depletion is present. The non-specific laboratory findings are worthy of mention. Anemia is present in some 84 per cent of cases; in the great majority (about 78 per cent) it is a typical hypochromic anemia undoubtedly due to inadequate intake or utilization of iron.¹⁰ In a relatively small number of patients macrocytic and hyperchromic anemia is found. It is likely that a specific type of liver damage plays an important part in the genesis of this type of anemia since it is much more frequent in the so-called alcoholic pellagra than in the endemic disease due to prolonged dietary inadequacy. It has been shown that the liver in fatal endemic pellagra is rich in the erythrocyte maturing factor. This observation would suggest that the hepatic as well as the gastric defect in pellagra is different from that in pernicious anemia. Plasma proteins are commonly reduced at the expense of the albumin fraction. This finding is probably entirely non-specific and indicative only of inadequate protein intake. Gastric achlorhydria is found in some 80 per cent of patients with pellagra and, as mentioned previously, may be of significance as a cause of progressive failure to extract vitamins from food. Since the introduction of histamine there has been no significant variation in the incidence of achlorhydria so the older observations on the frequency of its occurrence are probably valid.

Because it has been suggested that excessive formation of porphyrin with chronic porphyrinemia might account for the relation between the typical pellagrous dermatitis and exposure to sunlight, considerable attention has been paid to the presence of porphyrin in the urine of pellagrins. When the urine of patients with pellagra or with evidences of nicotinic acid deficiency without dermatitis, is tested by the "first method" of Hans Fischer or the modification proposed by Beckh, Ellinger and Spies¹² a positive reaction is obtained in almost every instance. The procedure consists in strongly acidifying (pH4) an aliquot of the 24 hour specimen of urine and extracting it with two volumes of ether by shaking. The ether extract is washed twice with half volumes of distilled water, then extracted with a small amount (about 1/10 volume) of 25 per cent hydrochloric acid. The positive reaction is the development of a pink to purple color in the acid extract. It was thought at first that this color was due to the presence of coproporphyrin but Watson¹³ and Dobriner and Rhoads¹⁴ have shown that there is no relation between the amount of coproporphyrin present in the urine and the depth of color developed. Neither is there relation between the intensity of color and the clinical manifestations of pellagra. Visible color is due largely to urosein and while excessive amounts of copropor-

pyrin are excreted in certain instances of pellagra, this test does not detect it. Though the original purpose of the test has not been fulfilled it remains useful since it is positive only rarely in conditions other than the pellagrous syndrome. The pathological basis of the reaction remains obscure though it is thought to indicate impairment of liver function.

During the past three years it has become possible to separate the various symptoms and signs of at least most of the specific avitaminoses contributing to the syndrome of classic pellagra by therapeutic tests with pure vitamins. When patients presenting the complete picture are maintained on a basal diet extremely poor in all vitamins but adequately supplemented with vitamins A, C and D, the available members of the B group can be added singly in large amounts and valid conclusions drawn from the resulting effect on certain groups of morbid phenomena. As had been suspected, the paresthesias, neuritic pains, diminished tendon reflexes, edema and tachycardia so often seen in pellagra are relieved by the administration of thiamin chloride.^{15, 16} Also, anorexia, flatulence and constipation often disappear during treatment with this vitamin.

When nicotinic acid is added, psychic manifestations of all grades are cured or greatly improved.^{17, 18, 19, 20} In a number of instances, impairment of hearing has been greatly relieved.^{9, 19} Appetite is often increased more strikingly than by thiamin; nausea and diarrhea are controlled promptly. The typical bright red, atrophic, frequently fissured or ulcerated tongue is blanched and often a rich growth of papillae is evident within 48 hours after treatment is begun. Stomatitis, esophagitis and lesions of the genitalia and rectal mucosa heal with equal rapidity even though secondary mycotic or spirillary infections are present. Typical dermatitis wherever located undergoes somewhat slower resolution but seldom requires more than ten days for healing. It is notable that seborrheic lesions are not cured. An apparently specific effect of nicotinic acid is the restoration of the acid secreting function of the gastric mucosa. This may follow a few weeks of treatment or may not occur until after many months of continuous administration of the vitamin. It is likely that this effect is important in the actual cure of pellagra since there is a direct relation between the incidence of relapse and the persistence of achlorhydria.²¹

During the first year of nicotinic acid therapy of pellagra it was noted that many patients whose glossitis, dermatitis and diarrhea were cured, retained certain lesions or acquired others as they were maintained on a basal diet supplemented with vitamins A, C, D and nicotinic acid. Seborrheic dermatitis of the face, the well known "shark-skin" follicular keratosis of the forehead, nose and malar eminences, redness and desquamation of the lips, fissures in the lips and at the commissures (the marginal stomatitis of Stannus²²) persisted when present and developed in not a few. In a large number it was noted that from three to six weeks after the cure of pellagrous glossitis the tongue acquired a striking purplish-red or magenta color and that the newly grown papillae became flattened or mushroom-

shaped, giving the organ a finely pebbled appearance. At the same time there was redness of the buccal surfaces of the lips and often complaint of burning and soreness of the mouth and tongue. At first these phenomena were interpreted as signs of relapse of pellagra but in December of 1938, Sebrell and Butler² reported the experimental production of the majority of these lesions by a diet deficient in riboflavin and cure following the administration of this vitamin. More recently it has been shown that extensive "seborrheic" dermatitis^{23,24} and various ocular symptoms and signs^{18, 23, 24, 25} are manifestations of riboflavin deficiency. The ocular disturbances are of particular interest because of their wide prevalence. Photophobia, burning and itching of the eyes, ocular fatigue and dimness of vision not improved by correction of refractive errors and often, poor vision in dim light are complaints of pellagrins which are not relieved by thiamin or nicotinic acid but which disappear quickly during the administration of riboflavin. Patients with such complaints are found to have varying grades of vascularization of the cornea, at first superficial, later, interstitial and often associated with corneal opacities. This "nutritional keratitis" is rapidly cured by riboflavin in adequate doses.

Of more clinical importance than pellagra are the formes frustes of the avitaminoses of the B group which occur as definite clinical entities, usually without dermatitis and often without atrophic glossitis, diarrhea or the other classic manifestations of the syndrome. These are often precipitated by infection or by certain therapeutic efforts and in the past have been regarded as evidence of "toxic states." Not infrequently they represent the effect of severe acute vitamin deficiency superimposed upon a mild chronic poly-avitaminosis. Alcoholism is a prominent cause of such conditions since the utilization of energy from alcohol involves the same coenzyme systems which are active in the metabolism of dextrose. The hypermetabolism of acute infections and hyperthyroidism are equally effective in producing exhaustion of the coenzymes. The therapeutic administration of large amounts of dextrose solutions by parenteral routes and the use of high carbohydrate diets and large amounts of insulin in the treatment of depleted diabetics⁴ produce an analogous imbalance between derivation of energy from carbohydrate and replacement of vitamins necessary for its normal metabolism. The rapidity with which depletion is produced precludes the incidence of pronounced anatomical changes so that many features of the classic disease are lacking.

The picture of acute thiamin deficiency resulting from alcoholism is so well known that the incidence of neuritic pain, nerve and muscle tenderness, motor and reflex disturbances or edema and tachycardia without apparent cause immediately suggests this etiology. It is not so widely recognized that maintenance on parenterally administered solutions of dextrose may produce an analogous condition. After four or five days of such treatment edema, neuritic pain, tender nerve trunks and motor weakness are not infrequent. Edema occurring during prolonged venoclysis or repeated large

intravenous infusions of dextrose solutions has long been attributed to the use of physiologic saline solution as the solvent for dextrose and the large intake of water and sodium has been blamed for edema. Simple waterlogging from the introduction of excessive amounts of fluids has been the accepted explanation of edema occurring when no sodium chloride was present in the infusion fluid. While it is quite possible to produce edema by overloading the vascular apparatus with fluids, particularly in feeble individuals, this phenomenon seems relatively unusual. In our experience every instance of "waterlogging" associated with tachycardia, neuritic pain or tenderness of the extremities has shown prompt diuresis and relief of pain and tenderness as well as slowing of the heart when adequate doses of thiamin were given. Severe peripheral neuritis with quadriplegia may follow the combined use of large amounts of nicotinic acid and insulin in the treatment of postoperative psychosis.⁶ Such therapeutic accidents emphasize the validity of the concept that "deficiency diseases" are essentially disturbances of the process of biological oxidation, the clinical manifestations depending on the particular stage of the utilization of energy from hexoses most affected. In the case of patients developing peripheral neuritis from large amounts of insulin and nicotinic acid, the mechanism seems obvious. Under the drive of large amounts of insulin, carbohydrate metabolism is tremendously increased, with an abundance of nicotinic acid (and probable reserves of riboflavin) the preliminary and intermediate stages of dehydrogenation proceed in the normal manner. In the final stage, decarboxylation of pyruvic acid fails because of lack of an adequate supply of diphosphothiamin (cocarboxylase) and the various clinical manifestations of beri-beri result.

Nicotinic acid deficiency without dermatitis is extremely common and frequently overlooked, even in localities where endemic pellagra is prevalent. It is highly probable that in a great majority of instances the symptoms and signs result from severe or almost total deprivation of the vitamin in individuals already in a borderline state of nutrition. Since the cerebral neurons seem to be particularly sensitive to the metabolic disturbances resulting from failure of coenzyme function, it is not surprising that psychic disorders predominate in this condition. Glossitis is frequent but often quite unlike that typical of pellagra. The red, rough, often partially coated tongue usually attributed to "toxic states" or to dehydration alone, the deeply fissured tongue or the geographic tongue have been seen so often in these patients that it seems justifiable to suspect that all such glossitides may be evidences of nicotinic acid deficiency. In many instances, however, the tongue is heavily coated, with neither papillary atrophy nor abnormal redness. Anorexia, nausea and vomiting are frequently the effects of avitaminosis as well as important contributors to its persistence and severity. Often, indeed usually, the relation of nicotinic acid deficiency to such common accompaniments of disease can be proved only by therapeutic test. Either psy-

chosis or glossitis may be the presenting manifestation; frequently they occur together.

It is common experience that many patients with infectious diseases such as pneumonia, erysipelas, osteomyelitis or any severe sepsis may develop glossitis, usually of the rough, red "toxic" type; occasionally the tongue is bright red and smooth. Mental confusion, delirium and "toxic psychoses" are almost equally frequent. It is customary in most hospitals to administer large amounts of dextrose solutions intravenously to patients with such conditions. Very often this treatment seems to aggravate the mental symptoms and the tongue and buccal mucosa become increasingly red sometimes with ulceration or the formation of pseudomembranes due to infection with moniliae or Vincent's organisms. Many times nausea and vomiting as well as soreness of the mouth and pharynx interfere with the taking of reasonably adequate nourishment. Even more often the combination of mental confusion or actual delirium and glossitis and stomatitis is seen in patients with complicated surgical conditions who from necessity are maintained for considerable periods by the parenteral administration of solutions of dextrose and physiologic saline solutions. All types of obstructive lesions of the gastrointestinal tract, acute cholecystitis, operations upon the stomach or bowel, all varieties of suppurative peritonitis and extensive infected wounds furnish frequent examples of this syndrome. It is seen very often too after emergency operations for urinary obstruction due to prostatism and here the type of operation seems to be unimportant. The factors which seem to be contributory to avitaminosis in these groups are fever, vomiting and the administration of large amounts of dextrose. Fever causes hypermetabolism with increased energy requirements; vomiting prevents the absorption of vitamins from any normal foodstuffs which may be taken. Glucose maintenance, though the only available method of alimentation in many instances, increases the utilization of coenzymes without furnishing any replacement.

A relatively infrequent but theoretically significant cause of avitaminosis is the use of a high carbohydrate diet and large amounts of insulin in the treatment of diabetics probably already in a borderline state of nutrition.⁴ We have seen signs and symptoms of vitamin deficiency develop under these circumstances in five instances. The patients were all severely diabetic and living under such economic stress that it was not possible for them to procure a diet even reasonably adequate in protein and fat. They were hospitalized for regulation and in each instance the carbohydrate intake was raised to approximate that of the home diet available. This resulted in a ration of some 280 gm. carbohydrate, 70 gm. protein and 70 gm. of fat and required an increase of about 50 units of insulin per day above the former dose. (Insulin is available from relief agencies though proper food cannot be obtained.) In each case delirium occurred on the fourth or fifth day of the increased carbohydrate and insulin regime. In the first two, this was attributed to hypoglycemia until blood sugar determinations were made. Glossitis typical of nicotinic acid deficiency developed simultaneously with

psychosis in four patients; the fifth had the purplish granular tongue of ariboflavinosis. All five were free from mental symptoms on the second day of treatment with nicotinic acid, the one patient who showed evidence of riboflavin deficiency also, proceeded to develop cheilosis with fissures at the commissures of the lips. Such cases seem to furnish strong confirmation of the theory that the physiologic basis of symptoms in the "B" avitaminoses is the derivation of energy from carbohydrate in excess of the available supply of vitamins. With great increase in the utilization of carbohydrate in the presence of adequate amounts of insulin, these diabetics rapidly exhausted their scanty supplies of nicotinic acid and riboflavin and developed rather severe and acute evidences of deficiency.

Perhaps the most common and important manifestations of severe and relatively acute nicotinic acid deficiency are the profoundly psychotic and stuporous conditions described by Cleckley¹⁹ and Jolliffe.²⁰ The clinical pattern is entirely variable; delusions, hallucinations, manic excitement as well as stupor and the encephalopathic state have been observed. Delirium tremens and post-alcoholic stupor have been seen to respond to massive doses of nicotinic acid and may tentatively be thought of as at least partly due to deficiency of this vitamin. The great majority of this severely psychotic group have shown no anatomical lesions of avitaminosis, glossitis and dermatitis being conspicuous by their rarity. This observation supports the suggestion of Jolliffe²⁰ that these states are due to total or subtotal deficiency produced with great rapidity so that there is not time for gross tissue changes to occur. A great many of our patients were elderly or senile with advanced arteriosclerosis. They presented a picture extremely familiar to all physicians practicing in general hospitals. Such patients are brought in unconscious; frequently they are known to have been living alone and in poor circumstances. Almost invariably the admitting diagnosis is uremia or some sort of cerebral accident. During the time required for completion of physical and laboratory examinations it is customary to give dextrose solutions intravenously to combat dehydration. Various tests show no evidence of severe renal insufficiency or of cerebral hemorrhage or thrombosis. Because such patients are not able to swallow, the extraoral administration of dextrose solutions is usually continued and after four or five days they die of bronchopneumonia. Treatment of such patients with nicotinic acid was tried rather empirically because there was frequent evidence of malnutrition and because the "red test" was positive in the urine. Rather surprisingly this high-mortality group was found to respond to the administration of nicotinic acid with rapid, often dramatic improvement. At least two of our patients presented the encephalopathic state described by Jolliffe²⁰ and, in his experience, due to chronic alcoholism. In this symptom complex, first emphasized by Bender and Schilder,²⁶ there is marked clouding of consciousness with variable cogwheel rigidities and uncontrollable grasping and sucking reflexes. Jolliffe was able to reduce the mortality in his large group of patients with this syndrome from 80 per cent in those treated with hy-

dration and supportive measures to 13.6 per cent in a series treated with large amounts of nicotinic acid. In our experience, 46 patients with stupor, delirium or encephalopathy had a mortality of 4.6 per cent as compared with 85 per cent of deaths in the years before nicotinic acid was used. In such patients it is entirely possible that the effect of nicotinic acid is twofold. We believe quite strongly that vitamin deficiency is the most important factor in the production of psychosis and its relief is a most important therapeutic objective. It is also probable that the vasodilator effect of nicotinic acid on arterioles results in a greatly increased supply of blood to the brain with much better supply of oxygen as well as pyridine nucleotides. This mechanism may apply to other organs and has been mentioned as a possible effect of arteriosclerosis in causing poor utilization of vitamins.

It must not be supposed that all stuporous or psychotic states of obscure etiology will respond to the administration of nicotinic acid or that any objection is raised to the use of dextrose solutions for hydration or parenteral nourishment. Reasonably thorough examination will reveal the common organic causes of delirium or stupor; when no such definite cause is evident, a therapeutic test with nicotinic acid is always justifiable. It is probably always wise to add nicotinic acid or sodium nicotinate to dextrose solutions when they are to be used for the prolonged hydration or nourishment of patients unable to swallow or retain food or fluids.

The amount of nicotinic acid required for the satisfactory treatment of the whole group of acute deficiencies is large. It has been our custom to give at least 600 mg. daily by mouth or through an indwelling stomach tube and 300 to 400 mg. by intramuscular or intravenous injection. Sodium nicotinate has been used almost exclusively for parenteral administration in amounts equivalent to the dose of nicotinic acid desired. When given intravenously it should be diluted with physiologic saline or with dextrose solution of desired strength to a concentration of about 0.05 per cent. (125 mg. of sodium nicotinate in 200 c.c. of diluent represents approximately this concentration.) For intramuscular injection a 10 per cent solution of sodium nicotinate has proved most satisfactory; the addition of 2 per cent of benzyl alcohol prevents pain at the site of injection. To avoid severe flushing reactions as well as waste of the vitamin from excretion it is advisable to limit single doses to 100 mg. of nicotinic acid or 125 mg. of the sodium salt.

The incidence of ariboflavinosis without definite clinical signs of other avitaminoses is high, suggesting that some conditioning factor yet unrecognized may prevent the utilization of this vitamin or create an unusual requirement for it. The studies of Steibeling²⁷ have indicated that there is widespread use of diets poor, if not actually inadequate, in riboflavin. In our experience, any or all of the factors which may cause nicotinic acid deficiency are effective in precipitating the signs of ariboflavinosis. These, as already noted, appear with great regularity in pellagrins treated with nicotinic acid alone and with no improvement in their diet. Many instances have been seen in persons using an apparently adequate diet and apparently free from

evident disease of the liver or gastrointestinal tract. The manifestations of acute riboflavin deficiency have not been adequately studied though there is reason to suspect that the state of collapse rapidly followed by death, which was formerly a common termination of severe pellagra, may be a manifestation of severe and possibly acute depletion.³² Such patients show many symptoms similar to those observed by Sebrell and his collaborators^{28, 29, 30} and by Street and Cowgill³¹ in dogs with the experimental avitaminosis. It may be important too that the liver in fatal pellagra is almost invariably extensively infiltrated with fat, resembling the "yellow liver" described by Sebrell and others in ariboflavinosis of dogs.^{10, 28, 30, 32}

Symptoms attributable to ariboflavinosis have already been mentioned. Lassitude and anorexia common to all the vitamin deficiencies are common; occasionally nausea is a prominent symptom. Ocular symptoms are exceedingly frequent and often precede oral lesions or dermatitis. Dimness of vision in poor light, blurred vision for distant objects, photophobia, "eye strain" and burning and itching of the eyes have been prominent complaints. These symptoms have been noted by previous observers. Spies, Vilter and Ashe¹⁶ noted such visual disturbances in some 70 per cent of a large series of pellagrins and noted that in some instances they were relieved by riboflavin. Spies³³ in another communication was inclined to attribute these symptoms to vitamin A deficiency. Pock-Steen²⁵ observed all the above mentioned complaints in a group of 109 patients with sprue and leiodystonia. He also observed mydriasis, disturbances of accommodation and evidences of keratitis in some. Such symptoms and signs were relieved in 78 of his series by small amounts of riboflavin. As noted before, these complaints are not relieved by correction of errors of refraction and in the past have frequently been attributed to focal infection, "toxic states" or over use of the eyes.

The gross signs of riboflavin deficiency are quite irregular in the sequence of their appearance. The seborrheic lesions of the ears, alar portions of the nose, forehead or malar eminences may precede or follow characteristic cheilosis, fissuring of the commissures of the lips or glossitis. In our experience, the specific glossitis and redness of the buccal surfaces of the lips have seemed to precede other signs in the majority of instances. The filiform, keratotic comedones clustered in the naso-malar grooves or over the forehead, malar eminences, alae nasi or chin have seemed to be rather late lesions. Occasionally severe dermatitis of seborrheic type may involve the whole face and neck.

A superficial vascularizing keratitis has been found to be the earliest and most constant manifestation of ariboflavinosis,²⁴ having been seen before any other definite lesion was visible. Mydriasis is a relatively uncommon accompaniment but is marked in patients with severe photophobia and may be the cause of this symptom. Some patients show irregular deposits of pigment on the surface of the iris which are apparently related to riboflavin deficiency. The occurrence of ocular lesions in human ariboflavinosis is not

surprising since it is such a prominent part of the picture in the experimental avitaminosis in rats. Day and his collaborators,^{34, 35} O'Brien,³⁶ Bourne and Pyke³⁷ and others have noted corneal opacities which cleared under treatment with riboflavin. Bessey and Wolbach³⁸ and Eckardt and Johnson³⁹ emphasized keratitis as an almost constant lesion. Bessey and Wolbach, using the slit lamp, were able to follow the development of keratitis during periods of experimental riboflavin deficiency in their rats and to observe resolution after treatment. Their report suggested slit lamp inspection as a method of early diagnosis in human beings.

Using the slit lamp, the earliest change observed in human subjects has been marked engorgement and proliferation of the limbic plexus with obliteration of the normal, narrow avascular zone between the extreme margin of the sclera and the cornea. Often each scleral digitation comes to be outlined by a large capillary loop. Recognition of this condition as abnormal followed the observation that such overfilling of the limbic plexus rapidly disappeared following the administration of riboflavin. If the deficiency is allowed to persist, fine capillaries sprout from the apices of the loops outlining the scleral digitations and invade the cornea just beneath the epithelium. These centripetally directed vessels soon anastomose to form a secondary arcade of capillary loops from which more capillaries sprout. This process may be repeated until an extensive superficial plexus is formed. Using retroillumination it is possible to see the newly formed capillaries before they become filled. Usually by the time secondary invading loops are formed, some capillaries arising from the limbic plexus invade the *substantia propria*. The process of corneal vascularization has not been followed further than this stage in patients but fully developed keratitis has been seen in which there were very large superficial and interstitial vessels with a dense plexus of fine capillaries throughout the *substantia propria*. Only a few vessels seem to strike deeply and run centripetally just inside Descemet's membrane. This absence of a dense posterior plexus seems to differentiate dietary keratitis from that occurring in syphilis where a posterior plexus is prominent. Diffuse superficial opacities have been seen in many patients with ariboflavinosis and interstitial opacities in a few. In two instances dense scars, apparently from old ulcers, were present. If the process in human beings is similar to that observed by Bessey and Wolbach in rats, the superficial and interstitial opacities are due to leukocytic infiltration of the subepithelial and deeper areas respectively. Posterior keratitic deposits have not been observed. Pigmentary changes in the iris are interesting though their significance is not yet understood. Many patients with gray irises have shown brown pigment spots not yet differentiated from "hazel spots" which disintegrated and disappeared during the administration of riboflavin. A number of those with brown irises showed a peculiar shaggy pigmentation of the entire anterior iridic membrane which obscured the normal architecture. This also was seen to disappear during treatment.

The specificity of these corneal and iridic changes as signs of aribo-

flavinoses seems to have been proved by their rapid resolution during administration of the vitamin. The amount necessary to produce rapid emptying of invading vessels and disappearance of opacities has varied from 3 to 15 mg. per day. Patients with early or slight vascular keratitis showed rapid improvement of symptoms and emptying of newly formed capillaries in the cornea with the smaller dose. Most patients were given 5 mg. daily; only those with severe keratitis received 15 mg. Emptying of very recently formed capillaries was observed after the ingestion of as little as 4 mg. of riboflavin; most patients required from 12 to 25 mg. before definite improvement was visible. Opacities tended to be slower in disappearing, seldom showing definite change before the sixth day of treatment. The time required for complete emptying of corneal vessels and clearing of opacities varied from six to fifteen days. Symptoms were quite regularly relieved by the fourth day of treatment. In a number of instances, treatment was withheld after maximal improvement had been attained. In no case was there failure of relapse. The time required for experimental relapse varied from two to eighteen days. Complete disappearance of newly formed corneal vessels has not been observed, though no case has been followed for more than seven months. While entirely empty of blood they remain visible by direct illumination as fine refractile lines and by retroillumination as coarser gray streaks. Spontaneous relapse during treatment has occurred, usually as a result of seemingly obvious causes. Fever from intercurrent infection, nausea and diarrhea from food poisoning and the incidence of pregnancy have seemed to be particularly potent. A few patients have relapsed without evident cause but have promptly been cured by increase in the dose of riboflavin. An interesting and as yet obscure phenomenon is the fact that relapse following withdrawal of the vitamin constantly results in a much more severe keratitis than that present before treatment was begun.

Several interesting and perhaps important observations have been made. Mydriasis occurring in patients with ariboflavinoses is quite constantly abolished while the vitamin is administered. The mechanism of this mydriasis is as yet unexplained. The pigmentary changes of the iris, while probably due to migration of melanophores to the anterior surface of the iris, are not regularly associated with classical iritis or evidence of congestion of the intrinsic plexus. More intriguing than any other phase of the experiment is the fact that several cases of "typical" syphilitic interstitial keratitis which showed no improvement or had come to a standstill after intensive antisymphilitic therapy have responded to the administration of riboflavin by relatively rapid emptying of all corneal vessels, the superficial and interstitial plexuses being the first to empty, the posterior requiring from five to 15 weeks of treatment to become free of blood. Dense anterior and interstitial opacities have cleared so that patients whose vision was less than 5/200 have attained as much as 15/20. Relief of photophobia in these cases has been remarkable; patients who wept constantly in the dark have been able to

endure full sunlight or the glare of photographic lamps after the ingestion of 15 to 30 mg. of riboflavin. It would seem that riboflavin may prove a valuable adjunct to the treatment of syphilitic keratitis though the mechanism of its action in this condition is not clear.

The rationale of riboflavin deficiency in the production of ocular symptoms and signs has been suggested by Bessey and Wolbach³⁸ and Kimble and Gordon.⁴⁰ The symptom, poor vision in dim light, may well be attributed to faulty utilization of vitamin A, which has been shown to occur in the absence of adequate supply of riboflavin. Photophobia is probably the effect of spastic mydriasis, for which no mechanism has been suggested. Poor distant vision probably depends on accommodation defect which is common in ariboflavinosis but is as yet unexplained. The mechanism of vascularizing keratitis is fairly obvious. Bessey and Wolbach suggested that in riboflavin deficiency the cells of the cornea lack enough of the vitamin to secure the transport of oxygen from the air through the cells of the epithelial layer to those of the *substantia propria*. In response to anoxemia of the *substantia propria*, capillaries spring from the limbic plexus to furnish oxygen transport directly from erythrocytes to the deeper layers of the cornea.

In the treatment of ariboflavinosis it is important to note that relatively large amounts of the vitamin are necessary. Steibeling²⁷ estimated that about 2 mg. is the normal daily adult requirement. We have found that 3 mg. is probably a minimal therapeutic dose and that most patients require 5 mg. and some as much as 15 mg. for rapid improvement. For specific effect it is necessary to use the pure synthetic vitamin since it is almost impossible to secure adequate intake otherwise. No satisfactory preparation for injection is available and it seems likely that absorption and utilization of riboflavin is much more likely to be diminished by conditioning factors than is that of any of the other B group vitamins. It is important also to protect all preparations of riboflavin from light since even short exposure may cause reduction to the inactive leukoflavin.

In conclusion it seems necessary to emphasize the fact that an adequate diet is the most important therapeutic measure in all avitaminoses. Regardless of the administration of pure vitamins or mixtures of them, sufficient amounts of protein and fat are essential to health and minerals must be supplied. It is particularly important to refrain from treating presenting symptoms due to a single predominating avitaminosis with large amounts of the specific vitamin. This procedure is almost certain to precipitate the manifestations of coincident subclinical deficiencies of other members of the group.

Many of the observations mentioned in this lecture were made possible by a grant in aid from the John and Mary R. Markle Foundation.

BIBLIOGRAPHY

1. ELVEHJEM, C. A., MADDEN, R. J., STRONG, F. M., and WOOLLEY, D. W.: Relation of nicotinic acid and nicotinic acid amide to canine blacktongue, *Jr. Am. Chem. Soc.*, 1937, lix, 1767.
2. SEBRELL, W. H., and BUTLER, R. E.: Riboflavin deficiency in man, *Pub. Health Rep.*, 1938, liii, 2282.
3. SEBRELL, W. H., and BUTLER, R. E.: Riboflavin deficiency in man, *Pub. Health Rep.*, 1939, liv, 2121.
4. SYDENSTRICKER, V. P., GEESLIN, L. E., and WEAVER, J. W.: Avitaminosis occurring in diabetic patients under insulin therapy, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2137.
5. SYDENSTRICKER, V. P., SCHMIDT, H. L., FULTON, M. C., NEW, J. S., and GEESLIN, L. E.: Treatment of pellagra with nicotinic acid, *South. Med. Jr.*, 1938, xxxi, 1155.
6. Author's unpublished observations.
7. HUBER, H., and VERZAR, F.: Phosphorylierung von Riboflavin durch Darmschleimhautextrakte und die Wirkung von Iodessigsäure darauf, *Helvet. chim. acta*, 1938, xxi, 1006.
8. SPIES, T. D., ARING, C. D., GELPERIN, J., and BEAN, W. B.: The mental symptoms of pellagra, *Am. Jr. Med. Sci.*, 1938, cxcvi, 461.
9. SELFRIDGE, G.: Nicotinic acid and the eighth nerve: preliminary report, *Ann. Otol., Rhin. and Laryng.*, 1939, xlviii, 39.
10. SYDENSTRICKER, V. P., and ARMSTRONG, E. S.: A review of 440 cases of pellagra, *Arch. Int. Med.*, 1937, lix, 883.
11. SYDENSTRICKER, V. P., SCHMIDT, H. L., GEESLIN, L. E., and WEAVER, J. W.: The liver in pellagra, *Am. Jr. Med. Sci.*, 1939, cxcvii, 155.
12. BECKH, W., ELLINGER, P., and SPIES, T. D.: Porphyrinuria in pellagra, *Quart. Jr. Med.*, 1937, vi, 305.
13. WATSON, C. J.: The urinary pigments in four cases of alcoholic pellagra, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 514.
14. DOBRINER, K., and RHOADS, C. P.: Quantitative determination of urinary coproporphyrin, *New England Jr. Med.*, 1938, ccix, 1027.
15. JOLLIFFE, N.: The diagnosis, treatment and prevention of B₁ deficiency, *Bull. New York Acad. Med.*, 1939, xv, 469.
16. SPIES, T. D., VILTER, R. W., and ASHE, W. F.: Pellagra, beri-beri and riboflavin deficiency in human beings, diagnosis and treatment, *Jr. Am. Med. Assoc.*, 1939, cxiii, 931.
17. MATTHEWS, R. S.: Pellagra and nicotinic acid, *Jr. Am. Med. Assoc.*, 1938, cxi, 1148.
18. SPIES, T. D., ARING, C. D., GELPERIN, J., and BEAN, W. B.: The mental symptoms of pellagra, their relief with nicotinic acid, *Am. Jr. Med. Sci.*, 1938, cxcvi, 461.
19. CLECKLEY, H. M., SYDENSTRICKER, V. P., and GEESLIN, L. E.: Nicotinic acid in the treatment of atypical psychotic states associated with malnutrition, *Jr. Am. Med. Assoc.*, 1939, cxii, 2107.
20. JOLLIFFE, N., BOWMAN, K. M., ROSENBLUM, L. A., and FEIN, H. D.: Nicotinic acid deficiency encephalopathy, *Jr. Am. Med. Assoc.*, 1940, cxiv, 307.
21. SYDENSTRICKER, V. P., SCHMIDT, H. L., FULTON, M. C., NEW, J. S., and GEESLIN, L. E.: Treatment of pellagra with nicotinic acid, *South. Med. Jr.*, 1938, xxxi, 1155.
22. STANNUS, H. S.: Deficiency diseases in Sierra Leone and pellagra, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1930, xxiii, 627.
23. SYDENSTRICKER, V. P., GEESLIN, L. E., TEMPLETON, C. M., and WEAVER, J. W.: Riboflavin deficiency in human subjects, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1697.
24. KRUSE, H. D., SYDENSTRICKER, V. P., SEBRELL, W. H., and CLECKLEY, H. M.: Ocular manifestations of ariboflavinosis, *Pub. Health Rep.*, 1940, Iv, 157.
25. POCK-STEEN, P. H.: Eye symptoms in patients with leiodystonia and sprue; aknephas-copia, *Geneesk. tijdschr. v. Nederl.-Indië*, 1939, lxxix, 1986.

26. BENDER, L., and SCHILDER, P.: Encephalopathica alcoholica, *Arch. Neurol. and Psychiat.*, 1930, xxix, 990.
27. STEIBELING, H. K., and PHIPARD, F.: Diets of families of employed wage earners and clerical workers in cities, U. S. Dept. Agric. Circular No. 507, Jan., 1939.
28. SEBRELL, W. H.: "Yellow liver" of dogs (fatty infiltration) associated with deficient diets, *Nat. Inst. Health Bull.*, 1933, 162.
29. SEBRELL, W. H., ONSTOTT, R. H., and HUNT, D. J.: The treatment of blacktongue with a preparation containing the "filtrate factor," and evidence of riboflavin deficiency in dogs, *Pub. Health Rep.*, 1937, lii, 427.
30. SEBRELL, W. H., and ONSTOTT, R. H.: Riboflavin deficiency in dogs, *Pub. Health Rep.*, 1938, liii, 83.
31. STREET, H. R., and COWGILL, G. R.: Acute riboflavin deficiency in the dog, *Am. Jr. Physiol.*, 1939, cxxv, 323.
32. FIELD, H., JR., and WISE, E. C.: Fatal probable riboflavin deficiency in man, *Jr. Clin. Invest.*, 1939, xviii, 474.
33. SPIES, T. D.: A note on the ocular symptoms and signs occurring from malnutrition in human beings, *Am. Jr. Med. Sci.*, 1939, cxcviii, 40.
34. DAY, P. L., LANGSTON, W. C., and O'BRIEN, C. S.: Cataract and other ocular changes in vitamin G deficiency; experimental study on albino rats, *Am. Jr. Ophth.*, 1931, xiv, 1005.
35. DAY, P. L., DARBY, W. J., and LANGSTON, W. C.: Identity of flavin with cataract-preventive factor, *Jr. Nutr.*, 1937, xiii, 289.
36. O'BRIEN, C. S.: Experimental cataract in vitamin G deficiency, *Arch. Ophth.*, 1932, viii, 880.
37. BOURNE, M. C., and PYKE, M. A.: Occurrence of cataract in rats fed on diets deficient in B₂, *Biochem. Jr.*, 1935, xxix, 1865.
38. BESSEY, O. A., and WOLBACH, S. B.: Vascularization of the cornea of the rat in riboflavin deficiency, with a note on corneal vascularization in vitamin A deficiency, *Jr. Exper. Med.*, 1939, lxix, 1.
39. ECKARDT, R. E., and JOHNSON, L. V.: Nutritional cataract and relation of galactose to appearance of senile suture line in rats, *Arch. Ophth.*, 1939, xxi, 315.
40. KIMBLE, M. S., and GORDON, E. S.: The importance of riboflavin and ascorbic acid in the utilization of vitamin A, *Jr. Biol. Chem.*, 1939, cxxviii, lii. (In *Proc. Am. Soc. Biol. Chem.*, April 26-29, 1939.)

FUNDAMENTAL PRINCIPLES IN THE ADJUSTMENT REACTIONS OF THE ORGANISM TO ANOXIA *

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A STUDY of the effects of anoxia on the human organism and on laboratory animals is of particular value to physiology and medicine because it lends itself well to demonstrating the interrelation of various organ systems in the body. This aspect of the problem will be stressed in the following discussions as well as some important clinical implications. Finally an attempt will be made to show which characteristics of the central nervous system are ultimately responsible for the adjustment reactions occurring in anoxia.

It is well known that under the influence of anoxia as induced by the breathing of suitable oxygen-nitrogen gas mixtures, the respiratory volume increases and the blood pressure is raised. Both reactions greatly contribute to an improvement of the oxygenation of the tissues and particularly of the brain. It is of great interest to show the interrelation of these two reactions. Numerous experiments conducted on dogs anesthetized with chloralose have shown that both respiratory and blood pressure responses increase with decreasing concentration of oxygen in the inhaled air (Gellhorn and Pollack²¹). Two different types of response can easily be distinguished. The first is characterized by a marked respiratory response and little or no alteration in the blood pressure; the other shows a small respiratory response and pronounced blood pressure effects. Figure 1 illustrates these two types. In both experiments 11 per cent oxygen was inhaled for five minutes. The blood pressure was recorded from the femoral artery and the respiratory

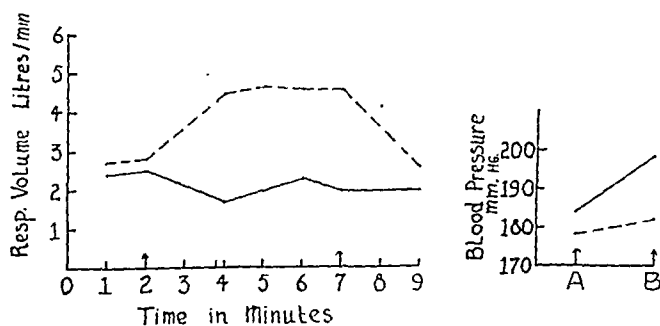


FIG. 1. Influence of inhalation of 11 per cent oxygen on blood pressure and respiration of two dogs narcotized with chloralose 100 mg./kg. intravenously. Seven per cent O_2 administered between the second and seventh minutes. On the right side changes in blood pressure: A: Blood pressure before anoxia; B: maximal rise of blood pressure during anoxia.

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volume was determined at intervals of one minute. Whereas the blood pressure rises 14 mm. in the experiment in which anoxia does not increase respiration, it rose only 4 mm. in the other experiment in which a marked respiratory response occurred.

It is very probable that the different reactions were due to the fact that the respiratory center was more depressed in one case than in the other although the anesthesia was the same in both cases. These observations make it likely that the respiratory response is the primary reaction of the organism to anoxia, and that only if this reaction is impeded or if the degree of anoxia is too severe to be adjusted by the respiratory response alone, the vasomotor reaction occurs leading to an improved circulation of brain and heart in proportion to the rise in blood pressure. Such an interpretation is supported by the observation that with increasing severity of anoxia the blood pressure reaction comes into action to an increasing degree. It is further illustrated by experiments in which in the same animal, the blood pressure response is studied under conditions of artificial respiration (pneumothorax).

Figure 2 shows how greatly the blood pressure rises on inhalation of 11 per cent oxygen after the respiratory adjustment has been eliminated by a pneumothorax. There was practically no change in blood pressure during anoxia when the respiratory adjustment was permitted to occur. When, however, a pneumothorax was made the blood pressure rose 35 mm. Hg in response to 11 per cent oxygen.²¹

Figure 3 illustrates the validity of our assumptions in an experiment in which the respiratory response to a mild anoxia was weak and consequently some rise in blood pressure occurred during inhalation of 11 per cent oxygen. Again the blood pressure reaction is distinctly increased after pneumothorax. Particularly interesting is the third record of figure 3 which was obtained when the respiratory minute volume under conditions of pneumothorax was reduced by nearly one half. The blood pressure level remained unchanged as long as air was inhaled, but when 11 per cent oxygen was administered the blood pressure rise was greatly increased over and above the reaction observed in the same animal when the respiratory volume was adjusted at a higher level. Moreover, marked signs of vagal stimulation occurred.

The blood pressure reaction to anoxia is also greatly modified under conditions which involve either anemia of the brain or of the whole organism. A certain degree of brain anemia may easily be established by temporary clamping of one or more of the main arteries to the brain.²¹ Such an experiment is illustrated in figure 4 in which at the beginning and at the end of the record, the blood pressure reaction to the inhalation of 4.5 per cent oxygen is shown, whereas in the two intervening experiments the effect of inhalation of 4.5 per cent oxygen on the blood pressure was studied under conditions of restricted brain circulation. In the first case both carotid arteries were clamped, in the second experiment both vertebral arteries were temporarily ligated. It is clearly seen that the temporary elimination of the

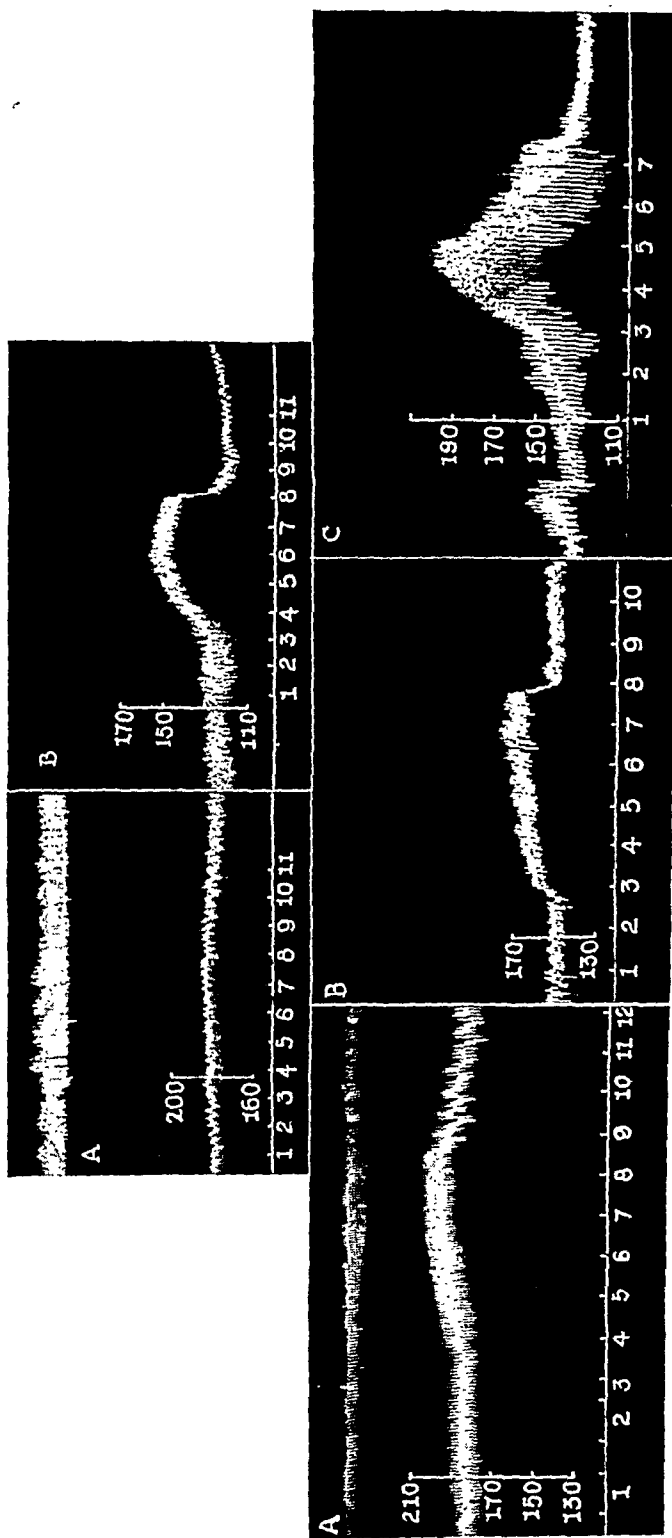


FIG. 2. *Above.* Dog 20. 1-10-40. 10.5 kg. 70 mg./kg. chloralose. Influence of inhalation of 11 per cent oxygen on the blood pressure (lower curve). A: natural respiration (upper curve), 11 per cent oxygen administered between 3 and 8. B: Pneumothorax; Respiratory volume—2.87 l/min.; 11 per cent oxygen between 3-8.

FIG. 3. *Below.* Dog 14. 12-21-39. 11.7 kg. 100 mg./kg. chloralose intravenously.
 A. Natural respiration. Eleven per cent oxygen administered for 5 min. from 3 to 8.
 B. Pneumothorax—11 per cent oxygen from 3 to 8. Respiratory minute volume kept at 2.5 l.
 C. As in B, but respiratory minute volume kept at 1.38 l.

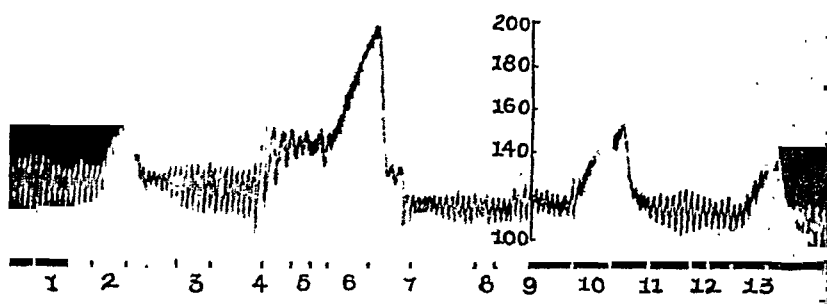


FIG. 4. Dog 7. 11-29-39. 8.4 kg. 100 mg./kg. chloralose intravenously. Influence of temporary clamping of carotid and vertebral arteries on the blood pressure response to inhalation of 4.5 per cent oxygen.

- 2—4.5 per cent O₂ for 60 seconds.
- 4—clamping of both carotid arteries below the bifurcation.
- 6—4.5 per cent O₂ for 60 seconds.
- 7—release carotids.
- 9—clamping of both vertebrals.
- 10—4.5 per cent O₂ for 60 seconds.
- 11—release vertebrals.
- 13—4.5 per cent O₂ for 60 seconds.

blood flow of the carotid arteries greatly intensifies the rise in blood pressure induced by the inhalation of 4.5 per cent oxygen. This may in part be due to the fact that after bilateral clamping of the carotid arteries the compensatory blood flow through the brain made possible by dilation of the cerebral vessels (Cobb⁴ and Fremont-Smith, Wolff and Lennox³¹ and others) cannot take place to the same degree in response to anoxia as it does under conditions of normal brain circulation. Consequently a more marked anoxia of the vasomotor system results which in conjunction with the stimulation of the chemoreceptor apparatus leads to an increased blood pressure. The elimination of the pressor receptors of the carotid sinus by the clamping of the common carotid arteries may also play a part in this reaction and this interpretation is supported by the observation that vagotomized animals respond with a still greater rise in blood pressure when subjected to anoxia under conditions of restricted brain circulation.

After temporary ligation of the vertebral arteries the blood pressure rise to anoxia is only slightly greater than is observed under control conditions, and in some cases the elimination of the vertebral circulation does not appreciably alter the blood pressure response.²¹

Whatever the ultimate explanation of the mechanism may be whereby the blood pressure response to anoxia is altered by reducing the blood flow through the brain it is interesting to show that moderate restrictions in brain circulation (clamping of one carotid artery or of one or two vertebral arteries) may so adequately be compensated by increased rate of blood flow (Rein²⁹) that no change in the blood pressure response to anoxia is seen when compared with that observed when all arteries are open. If, however, both carotid arteries are clamped, a more adequate circulation through the brain is secured by the increased blood pressure response to anoxia.

140

100 Mm. Hg

80

60

40

20

0

3:26 3:27 3:29 3:33 3:56 3:59

7.2% O₂

Air

The first and last record show the rise of blood pressure on increasing the intracranial pressure to the blood pressure level under control conditions. The second and third curves show the effect of anoxia induced by inhalation of 7.2 per cent oxygen on this reaction.

tion in the blood supply affecting the whole brain (experiments with restricted brain circulation) aggravates the blood pressure response to anoxia. Similarly, it is found that anoxia intensifies the effects of local anemia of the brain stem (experiments with increased intracranial pressure). Not only local anemia acts in this way, but general anemia also sensitizes the medullary centers to anoxia. Figure 6 shows that after successive bleedings both blood pressure and respiratory responses greatly increase during inhalation of 7 per cent oxygen. Here again is shown that a marked alteration in blood pressure response to anoxia is seen only after considerable loss of blood although the respiratory response increases quite markedly to lesser degrees of hemorrhage.²¹

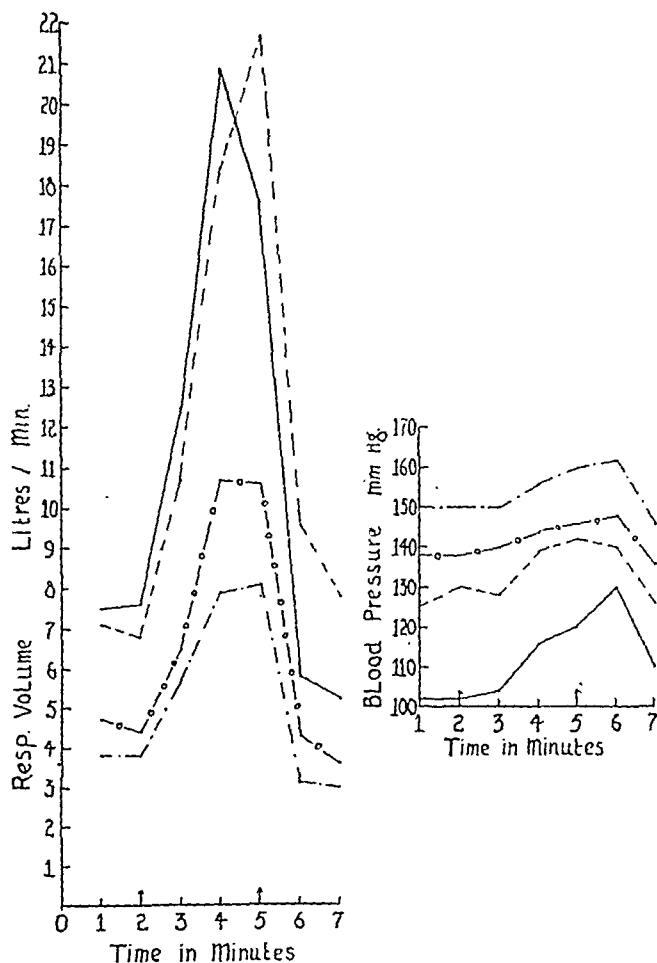


FIG. 6. Dog 43. 4-19-40. 12.5 kg.; 70 mg. chloralose intravenously. Effect of progressive hemorrhage on the reaction of blood pressure and respiration to the inhalation of 7 per cent oxygen for 3 min. (between the arrows at 2 and 5).

- . . . - Prior to the bleeding
- o - o - After loss of 9 per cent of calculated blood vol.
- - - - After loss of 13 per cent of calculated blood vol.
- After loss of 28.5 per cent of calculated blood vol.

The experiments which were cited illustrate under a variety of conditions three phenomena. They show

1. That the respiratory response to anoxia is a finer indicator of this condition than is the blood pressure.
2. That the blood pressure response to anoxia depends, other conditions being equal, on the degree of the respiratory response.
3. That both respiratory and circulatory responses to anoxia increase in conditions involving a reduction of blood supply to the medulla oblongata or to the whole brain. Similar effects are produced by a general anemia induced by bleeding.

As to the nature of the respiratory and blood pressure response only a

brief statement can be made. Heymans²⁵ and many other authors have shown that the increased respiratory response to anoxia is due to the action of the diminished oxygen tension of the blood on the chemoreceptors in the sino-aortic area since after elimination of the chemoreceptors respiration gradually fails. The organization of the vasomotor center is quite similar. Gellhorn and Lambert²⁰ showed that even under conditions of artificial respiration the blood pressure falls in anoxia after the buffer nerves have been eliminated, whereas in their presence the blood pressure rises on inhalation of oxygen-nitrogen mixtures (figure 7). This result is so typical in the dog that the fall in blood pressure during anoxia may be used as a test indicating complete removal of carotid sinus and depressor nerves.*

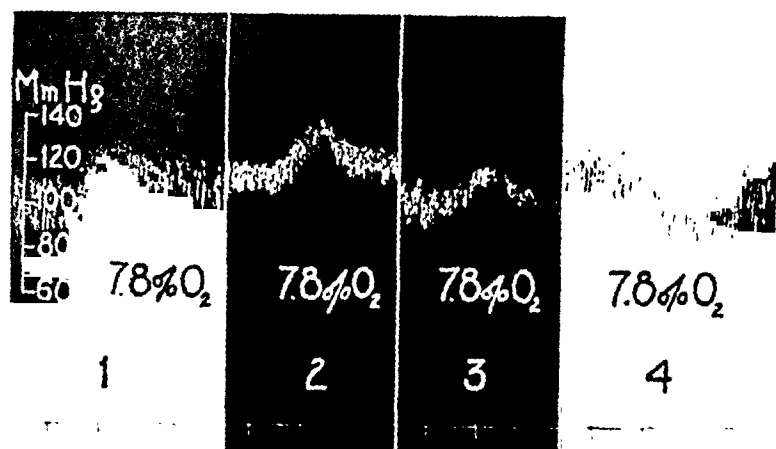


Fig. 7. The effect of vagotomy alone and vagotomy plus carotid sinus denervation on the blood pressure reaction of a dog to oxygen deficiency. Sodium amytal, 55 mg. per kilo; artificial respiration. Upper tracing represents blood pressure; lower tracing, signal indicating the period of administration of the gas mixtures. No. 1: Intact animal: 7.8 per cent oxygen administered for a period of 60 seconds. (Between 1 and 2, the right vagus nerve was cut in the neck.) No. 2: 7.8 per cent oxygen administered for a period of 60 seconds. (Between 2 and 3, the left vagus nerve was cut in the neck.) No. 3: 7.8 per cent oxygen administered for a period of 60 seconds. (Between 3 and 4, the carotid sinuses were denervated.) No. 4: 7.8 per cent oxygen administered for a period of 60 seconds. (From E. Gellhorn and E. Lambert.²⁰)

The regulatory processes which are evoked by anoxia are gradually weakened by the loss of carbon dioxide which accompanies the increased respiratory ventilation. It is therefore of considerable interest to call attention to the fact that in the human organism, anoxia may frequently be accompanied by an increased carbon dioxide tension in the blood as, for instance, in conditions of muscular exercise, or it may gradually lead to an accumulation of carbon dioxide if the circulatory adjustment breaks down. Thus it has been found that in the early stages of pneumonia a pure anoxia prevails, but at later stages of this disease due to circulatory impairment, the carbon dioxide tension in the blood rises (Meakins and Davis²⁶).

It seems to be of importance to distinguish between anoxia which is ac-

* Concerning details and bibliography cf. Gellhorn and Lambert.

accompanied by a fall in the carbon dioxide tension of the blood due to the compensatory increase in respiration and the condition of asphyxia which is characterized by a fall in oxygen and a rise in the carbon dioxide tension of the blood.

Asphyxia produced by clamping of the trachea causes such a rapid fall in oxygen and marked rise in carbon dioxide tension that after a brief excitatory state characterized by a rise in blood pressure and increased respiration both respiration and circulation fail. If, however, carbon dioxide is being accumulated only to a lesser degree thereby preventing the harmful effects of acapnia which ordinarily accompanies anoxia the adjustment reactions to anoxia are greatly strengthened. This can be shown in the human by studying the influence of inhaling 8.5 per cent oxygen with or without the presence of carbon dioxide. If the experiment is conducted in erect posture the systolic blood pressure falls within a few minutes and collapse may ensue.¹¹ But the same subject may easily tolerate this low oxygen concentration when the ill effects of acapnia are prevented by carbon dioxide.

On the basis of such experiments moderate asphyxia may be considered a final attempt of the organism to rid itself of the anoxia. This may be accomplished by the fact that the blood pressure rise in response to a given oxygen tension is markedly enhanced by even small amounts of carbon dioxide which in itself has no effect on the blood pressure (Gellhorn and Lambert,²⁰ Raab²⁷). The loss in muscle tone which accompanies anoxia and which is responsible for an insufficient venous return to the heart may be offset by small amounts of carbon dioxide. This was shown (Gellhorn and Hamilton¹⁶) by employing the direct method of measuring muscle tone by which Henderson²⁴ showed that carbon dioxide increases the muscle tone. The respiratory response to a given oxygen tension is also increased in the presence of small concentrations of carbon dioxide in inhaled air (Dill⁶).

Finally it is known that the sympathetico-adrenal system which so greatly aids in the improvement of the circulation of the brain and heart is called into action to a much greater extent under conditions of asphyxia than in an anoxia of the same degree. This can be demonstrated by a comparative study of the influence of anoxia and asphyxia on the blood sugar of unanesthetized rabbits.^{20a} Figure 8 shows that the blood sugar rises much more on inhalation of 7 per cent oxygen plus 4.5 per cent carbon dioxide than on inhalation of 7 per cent oxygen alone in spite of the fact that carbon dioxide itself does not cause any hyperglycemia. These experiments seem to indicate that the most effective treatment of anoxia would consist of the administration of carbon dioxide in oxygen (cf. Henderson²⁴) but only direct clinical studies can decide questions of therapy.

The greater reaction of the blood pressure and respiration and of the sympathetico-adrenal system to anoxia in the presence of carbon dioxide makes it highly probable that functions of the brain may withstand anoxia better when it is not accompanied by any decrease in the carbon dioxide tension in the blood. It seems rather probable that even slight increases in the

carbon dioxide tension of the blood may improve brain circulation in anoxia. Studies on various functions of the brain performed in humans and laboratory animals under conditions in which gases low in oxygen are inhaled either with or without some excess of carbon dioxide show indeed that brain functions are much better preserved when acapnia is avoided.^{8, 9, 10, 12, 13, 18, 19}

The effects resulting from inhaling 8.5 per cent oxygen with and without 3 per cent carbon dioxide are most marked when the highest cortical functions are investigated. It was seen that whereas during inhalation of 8.5 per cent oxygen mental functions involved in the addition of two digits are markedly impaired as shown by the increase in the number of errors, and in the time necessary to perform these operations, the same degree of anoxia

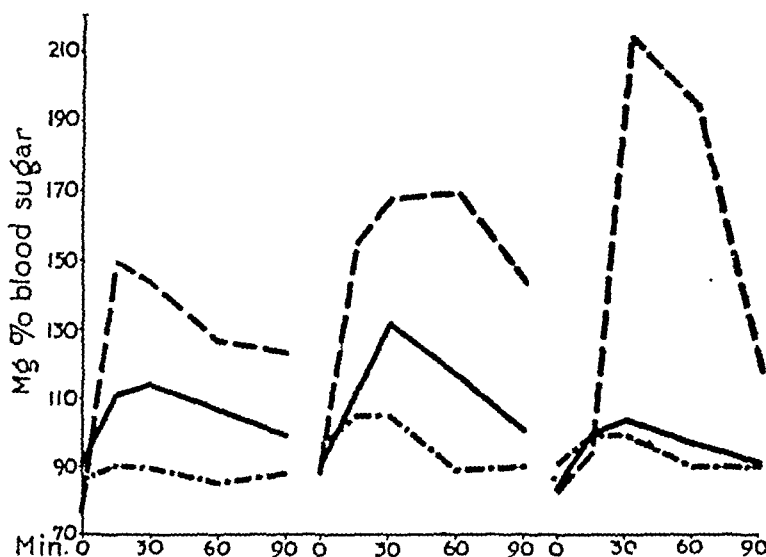


FIG. 8. The influence of CO₂ and oxygen lack on the blood sugar of rabbits. The gases were administered from Douglas bags for 90 minutes.

Abscissa: Time in minutes.

Ordinate: Blood sugar in mg. per cent.

— During inhalation of 7 per cent O₂.

..... During inhalation of 5.4 per cent CO₂.

----- During inhalation of 7 per cent O₂ + 5.4 per cent CO₂.

(From E. Gellhorn and A. Packer, *Proc. Soc. Exper. Biol and Med.*, 1939, xlii, 475.)

remained ineffective when 3 per cent carbon dioxide was inhaled at the same time. Similarly it was found that memory suffered much in anoxia although practically no deficiency was found when the anoxia test was carried out in the presence of 3 per cent carbon dioxide.¹³ Pathological deviations were revealed in association tests in anoxia but were absent when 8.5 per cent oxygen plus 3 per cent carbon dioxide were inhaled. Disturbances in mood were frequently observed during anoxia but failed to appear when acapnia was prevented by the simultaneous inhalation of carbon dioxide.¹⁵

A number of sensory tests were carried out and showed similar results. Visual function was impaired in anoxia but the presence of carbon dioxide

prevented its occurrence.⁹ Brain stem reflexes induced by caloric stimulation were investigated in the rabbit and it was found²² that the decrease in intensity of nystagmic movements observed in anoxia failed to appear when the rabbits inhaled the same percentage of oxygen in the presence of 4 to 5 per cent carbon dioxide.²² Disturbances in muscular coördination progressing with increasing duration of the anoxia period are best revealed in writing (figure 9). They are in sharp contrast with the results obtained when the same gas mixture was inhaled in the presence of 3 per cent carbon dioxide.¹³

These experiments prove that on account of the synergistic action of oxygen lack and carbon dioxide on respiratory and autonomic functions the

1 chair	26 bone	1 tree	26 taste
2 room	27 deep	2 shade	27 hard
3 box	28 room	3 bed	28 amon
4 isolation	29 woman	4 color	29 town
5 woman	30 base	5 shutter	30 town
6 narrow	31 surface	6 statue	31 beach
7 hard	32 United States	7 man	32
8 apple	33 print	8 color	33 noise
9 valley	34 black window	9 airplane	34 man
10 top	35 print	10 old	35 young
11 cat	36 color	11 test	36 pad
12 leg	37 night	12 book	37 distance
13 bed	38 white	13 but	38 cover
14 finger	39 room	14 bright - 0.11	39 rope
15 long	40 print young	15 stream	40 young
16 apple	41 wall	16 shy	41 silver
17 moth	42 men	17 man	42 sheep
18 rough	43 apple	18 church	43 noise
19 order	44 universe	19 steamship	44 lake
20 leg	45 street	20 ball	45 water-sim beside
21 Andy	46 sailor	21 wood	46 nitrogen
22 trail	47 salad	22 pants	47 chicken
23 dress	48 bed	23 catholic	48 up
24 brown roller	49 beach	24 card	49 up
25 train	50 pump	25 young	50 old

FIG. 9. Writing in an association test. (From E. Gellhorn, Am. Jr. Psychiat., 1937, xciii, 1413.) 9a: The influence of the inhalation of $8\frac{1}{2}$ per cent oxygen plus 3 per cent carbon dioxide. 9b: The influence of the inhalation of $8\frac{1}{2}$ per cent oxygen.

brain circulation is restored to such a degree as to offset completely, within certain limits, the effects of oxygen lack on the brain.

The reactions described thus far tend to improve the oxygenation of the tissues by increasing the oxygen tension in the alveolar air and by improving circulation in brain and heart. Many other subsidiary reactions take place which work in the same direction. They cannot be discussed here, but the contraction of the spleen increasing the number of circulating red blood cells (Barcroft¹), the opening of heretofore closed alveoli (Verzár³⁰), the more rapid unloading of the oxygen in the erythrocytes in the presence of increased carbon dioxide concentrations such as may occur in asphyxia may be men-

tioned. All these reactions improve the oxygenation of the tissues by facilitating transportation of oxygen to the tissues in anoxia.

These reactions are effectively supplemented by others which tend to reduce the oxygen demands of the tissues. It is well known that the metabolism of the organs depends on the temperature. A lowering in the body temperature would be a most effective means of reducing oxygen demands and thereby allowing the organism to continue its function under conditions of diminished oxygen supply. Such a reaction indeed occurs (Behague,² Chevillard and Mayer^{2a}) and is particularly well established in small animals with a relatively large surface area of the body (Gellhorn and Janus¹⁷). It is interesting to note that in the presence of carbon dioxide, the fall in body temperature induced by anoxia is greatly increased, as figure 10 indi-

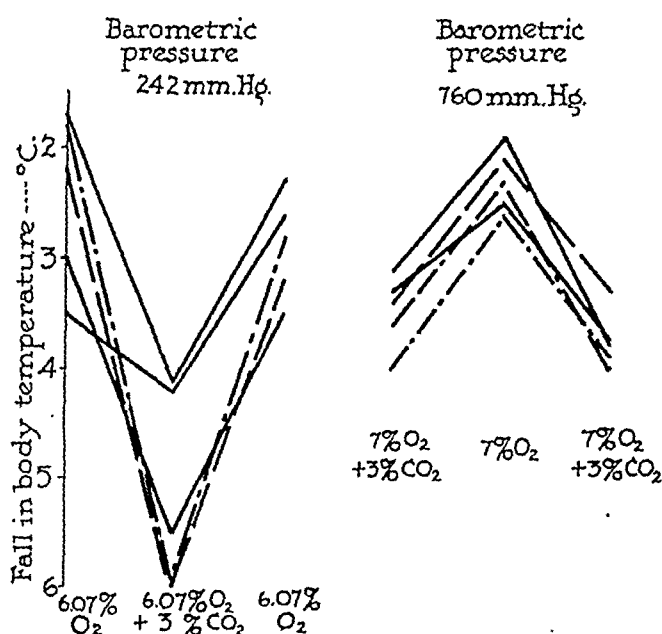


FIG. 10. The influence of a reduction in the O_2 -tension in the inhaled air with and without 3 per cent CO_2 on the body temperature of the rat. Duration of each experiment 55 minutes.

Ordinate: Fall in body temperature in degrees C.

Abscissa: Composition of the gas mixtures. In the left curve the reduction in O_2 -tension was obtained by reduction in barometric pressure, whereas in the experiments represented by the right curve the barometric pressure was normal and the O_2 concentration was obtained by dilution with nitrogen. (From E. Gellhorn, *Am. Jr. Physiol.*, 1937, cxx, 190.)

cates.¹⁴ This would mean that the conversion of anoxia into asphyxia improves not only the conditions for the transportation of oxygen to the tissues but also reduces more effectively the tissue metabolism than is accomplished by anoxia alone. Observations of Rein²⁸ showing that inhalation of carbon dioxide reduces the basal metabolism in the human in spite of increased respiratory activity seem to support this conclusion.

It is well known that anoxia and carbon dioxide depress somatic excit-

ability at cortical, subcortical and spinal levels, but the same factors stimulate respiratory and vasomotor centers, anoxia by its action on the chemoreceptors and carbon dioxide also directly. The possible causes of this discrepancy were investigated in order to find a clue to the mechanisms underlying adjustment reactions in anoxia. For this purpose experiments were performed which allow one to compare autonomic and somatic reflexes at approximately the same level of the central nervous system.

As a medullary reflex, the linguo-maxillary reflex was chosen. It is elicited by stimulating the endings of the lingual nerve in the tongue with condenser discharges and recording the contractions of the digastric muscle which is innervated by the motor branch of the trigeminal nerve. Respiration and blood pressure were recorded at the same time. Most of the experiments were conducted on cats anesthetized with chloralose which maintains well the reflexes mediated by the carotid sinus and arch of the aorta. It was found that anoxia decreases reversibly somatic excitability as measured by the linguo-maxillary reflex (Greenberg and Gellhorn²³). At the same time respiration is markedly increased and the blood pressure rises. Similarly it is found that asphyxia induced by clamping of the trachea inhibits the linguo-maxillary reflex while stimulating the respiration and blood pressure. The effects of anoxia and carbon dioxide on the somatic reflex are not altered by denervation of the carotid sinus and bilateral vagotomy although it is well known that the blood pressure and respiratory response is depressed in the "denervated" animal in anoxia. The experiments seem to point out that the chemoreceptors of the buffer nerves do not exert an excitatory influence on the somatic but only on the autonomic and respiratory centers.

Similar results were obtained in cats in which the hypothalamus was stimulated and the contraction of the nictitating membrane was recorded (Carlson,³ Darrow and Gellhorn). In a number of experiments central stimulation of the hypothalamus and peripheral stimulation of the cephalad end of the cut cervical sympathetic were performed in order to evaluate the peripheral and central effects of anoxia. It was observed that under these conditions only the central excitability greatly increased. It is interesting to point out that the movements of the extremities which ordinarily accompany hypothalamic stimulation gradually disappear under anoxia while the contraction of the nictitating membrane increases. This seems to indicate that anoxia decreases somatic but increases autonomic excitability also at the hypothalamic level. Moreover, it was found that during anoxia the threshold for somatic movements is markedly increased.

Two explanations seem to be possible for the differential effects of anoxia on somatic and autonomic excitability. First that the somatic centers are more sensitive to these agents than are autonomic centers. Second that the effects presented are not the results of a direct alteration of hypothalamic or medullary excitability but due to release from higher inhibitory centers. In this case it must be assumed that not the same degree of inhibition is exerted

on somatic and autonomic centers. Experiments on decerebrate cats seem to refute this assumption since in these animals also anoxia causes an increase in respiration and raises the blood pressure while decreasing the linguo-maxillary reflex.

These investigations seem to indicate that the autonomic centers are less sensitive to anoxia than are the somatic centers. They may therefore respond to anoxia with a heightened excitability whereas somatic centers show this effect only temporarily and pass then into a phase of diminished excitability. This difference in excitability accounts for the adjustment reactions occurring under conditions of anoxia and asphyxia. It is interesting to note that the respiratory center shows functionally a greater similarity to sympathetic than to other somatic centers.

SUMMARY

Adjustment reactions to anoxia were studied in humans and laboratory animals with emphasis on respiration and circulation. The results were as follows:

1. It was found that with decreasing oxygen concentration in the inhaled air, both respiratory volume and blood pressure increased progressively.

The blood pressure response is closely related to the respiratory response, inasmuch as in mild degrees of anoxia a respiratory response occurs without alteration in blood pressure. If, however, the respiratory response is poor or artificially curtailed by pneumothorax the blood pressure rises markedly in proportion to the reduction in respiration.

2. The blood pressure rise to a given degree of anoxia is markedly increased when the blood flow through the brain is diminished by temporarily clamping either the carotid or the vertebral arteries. The occlusion of the former is far more effective than that of the latter, which may be due not only to the greater amount of blood supply by the carotid arteries as compared with the vertebrals, but also to the elimination of the carotid sinus receptors in the experiment involving occlusion below the bifurcation. Anemia of the medulla induced by increased intracranial pressure causes a greater increase in blood pressure in anoxia than under control conditions.

Finally it was found that general anemia induced by progressive bleeding increases blood pressure and respiratory response to anoxia, although the blood pressure level was not significantly altered by the withdrawal of blood.

3. If the effects of acapnia which ordinarily accompany anoxia are prevented by the inhalation of small concentrations of carbon dioxide together with the oxygen-nitrogen gas mixture, it is found that blood pressure rise and respiration are markedly increased over and above the values obtained in pure anoxia. Moreover, it is found that the addition of carbon dioxide makes anoxia a more powerful stimulant of the sympathetico-adrenal system than is anoxia per se. These observations seem to indicate that a moderate

retention of carbon dioxide in anoxia elicits more powerful adjustment reactions to anoxia than does oxygen lack alone. This holds true not only for those reactions which improve the transport of oxygen to the tissues, but also for those processes which reduce the oxygen demands of the tissues by reduction of the temperature of the body. The better oxygenation of the tissues in asphyxia produced by the inhalation of oxygen-nitrogen mixtures containing some excessive carbon dioxide is illustrated by the fact that various functions of the brain are better preserved under these conditions than in similar experiments involving anoxia alone.

4. The fundamental observation that the vasomotor center is excited by anoxia while other cerebrospinal functions, except those involving the respiratory apparatus, are depressed, seems to be due to the fact that the sensitivity of autonomic centers to anoxia is considerably less than that of somatic centers. This may cause autonomic centers to react with signs of marked increased activity while somatic centers are depressed. This interpretation is supported by experiments in which various autonomic and somatic functions are studied under the influence of anoxia.

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BIBLIOGRAPHY

1. BARCROFT, J.: Features in the architecture of physiological function, 1934, New York.
2. BEHAGUE, P., GARSAX, and RICHET, FILS, C.: Modifications thermiques observées sur le lapin, soumis à la depression atmosphérique, *Compt. rendu Soc. biol.*, 1927, xcvi, 766.
- 2a. CHEVILLARD, L., and MAYER, A.: Recherches sur l'influence de la tension d'oxygène sur les échanges; influence de la tension de l'oxygène contenu dans l'air inspiré sur les échanges gazeux de la souris, *Ann. Physiol.*, 1935, xi, 225.
3. CARLSON, H. B., DARROW, C. W., and GELLHORN, E.: Physiological and pharmacological studies on the hypothalamus, *Am. Jr. Physiol.*, 1940, cxxix, 329.
4. COBB, S., and FREMONT-SMITH, F.: The cerebral circulation. XVI. Changes in the human retinal circulation and in the pressure of the cerebrospinal fluid during inhalation of a mixture of carbon dioxide and oxygen, *Arch. Neurol. and Psychiat.*, 1931, xxvi, 731.
5. CUSHING, H.: *Bull. Johns Hopkins Hosp.*, 1901, xii, 290.
6. DILL, D. B., and ZAMCHECK, N.: Respiratory adjustments to oxygen lack in the presence of carbon dioxide, *Am. Jr. Physiol.*, 1940, cxxix, 47.
7. GELLHORN, E.: Value of carbon dioxide in counteracting oxygen lack, *Nature*, London, 1936, cxxxvii, 700.
8. GELLHORN, E.: The effect of oxygen lack, variations in the carbon dioxide content of the inspired air, and hyperpnea on visual intensity discrimination, *Am. Jr. Physiol.*, 1936, cxv, 679.
9. GELLHORN, E.: The effectiveness of carbon dioxide in combating the changes in visual intensity discrimination produced by oxygen deficiency, *Am. Jr. Physiol.*, 1936, cxvii, 75.
10. GELLHORN, E.: The integrated action of the organism exemplified by the studies on anoxemia, *Sigma Xi Quart.*, 1937, xxv, 156.
11. GELLHORN, E.: Circulatory studies on anoxemia in man with respect to posture and carbon dioxide, *ANN. INT. MED.*, 1937, x, 1267.

12. GELLHORN, E.: On the mechanism by which carbon dioxide offsets the effect of oxygen deficiency, *Proc. Physiol. Soc. (Memphis)*, 1936, p. 60.
13. GELLHORN, E.: The influence of carbon dioxide in combating the effect of oxygen deficiency on psychic processes with remarks on the fundamental relationship between psychic and physiologic reactions, *Am. Jr. Psychiat.*, 1937, xciii, 1413.
14. GELLHORN, E.: Oxygen deficiency, carbon dioxide and temperature regulation, *Am. Jr. Physiol.*, 1937, cxx, 190.
15. GELLHORN, E.: Unpublished experiments.
16. GELLHORN, E., and HAMILTON, S.: Unpublished experiments.
17. GELLHORN, E., and JANUS, A.: The influence of partial pressure of oxygen on body temperature, *Am. Jr. Physiol.*, 1936, cxvi, 327.
18. GELLHORN, E., and JOSLYN, A.: The influence of oxygen want, hyperpnea and carbon dioxide excess on psychic processes, *Jr. Psychol.*, 1936, iii, 161.
19. GELLHORN, E., and KRAINES, S.: The influence of hyperpnea and of variations in the oxygen and carbon dioxide tension of the inspired air on word associations, *Arch. Neurol. and Psychiat.*, 1937, lxxxiii, 266.
20. GELLHORN, E., and LAMBERT, E.: The vasomotor system in anoxia and asphyxia, 1939, The University of Illinois Press, Urbana.
- 20a. GELLHORN, E., and PACKER, A.: Comparison of the influence of anoxia and asphyxia on blood sugar, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 475.
21. GELLHORN, E., and POLLACK, F.: Unpublished experiments.
22. GELLHORN, E., and STORM, L. F. M.: The influence of hyperventilation and of variations of the oxygen and carbon dioxide tension in the inspired air on galvanic nystagmus, *Acta oto-laryngol.*, 1938, xxvi, 387.
23. GREENBERG, R., and GELLHORN, E.: Studies on the linguo-maxillary reflex, *Am. Jr. Physiol.*, 1940, cxxix, 367.
24. HENDERSON, Y.: *Adventures in respiration*, 1938, Williams' and Wilkins, Baltimore.
25. HEYMANS, C., BOUCKAERT, J. J., and REGNIERS, P.: *Le sinus carotidien*, 1933, Doin, Paris.
26. MEAKINS, J. C., and DAVIS, H. W.: *Respiratory function in disease*, 1925, Edinburgh.
27. RAAB, W.: Central vasomotor irritability. Contribution to the problem of essential hypertension, *Arch. Int. Med.*, 1931, xlvii, 727.
28. REIN, H.: Die Möglichkeit zentralnervöser Regulierung des oxidativen Gesamtstoffwechsels im Warmblüterorganismus durch Kohlensäure, *Nachr. Ges. Wiss. Gottingen Math.-Physik. Kl. 2*: No. 14, 1936.
29. REIN, H.: *Ergebn. d. Physiol.*, 1931, xxxii, 49.
30. VERZAR, F., and JEKER, L.: Die physiologischen Atelektasen der Lunge, *Pflüger's Arch. f. d. ges. Physiol.*, 1937, ccxxxviii, 379.
31. WOLFF, H. G., and LENNOX, W. G.: Cerebral circulation. XII. The effect on pial vessels of variations in the oxygen and carbon dioxide content of the blood, *Arch. Neurol. and Psychiat.*, 1930, xxiii, 1097.
32. YESINICK, L., and GELLHORN, E.: Studies on increased intracranial pressure and its effects during anoxia and hypoglycemia, *Am. Jr. Physiol.*, 1939, cxxviii, 185.

HEMOLYTIC STREPTOCOCCAL PNEUMONIA AND EMPYEMA; A STUDY OF 55 CASES WITH SPECIAL REFERENCE TO TREATMENT*

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It is now well established that at least 85 to 90 per cent of all cases of pneumonia are due to pneumococcal infections and, of these, at least 80 per cent are caused by a relatively small number of specific types (I, II, III, V, VII, VIII, and XIV). Other microorganisms, such as *Streptococcus hemolyticus*, *Staphylococcus aureus*, *Bacillus Friedlander*, are usually responsible for the remaining cases. The hemolytic streptococcus is the cause of between 3 and 5 per cent of all cases of pneumonia although its frequency varies from time to time, depending somewhat upon the predisposing factors and the existence of epidemics of respiratory infections which create favorable conditions for the invasion of the organisms.

As a part of an investigation of hemolytic streptococcal infections, 55 cases of infection of the lungs and pleura were studied. In particular, we were concerned with the determination of the specific types of hemolytic streptococcus causing these infections and the effect of the newer chemotherapeutic agents in treatment.

ANALYSIS OF CASES

Etiology and Predisposing Factors. Hemolytic streptococcal pneumonia occurs most often following epidemic influenza or measles; less often it is associated with pneumococcal infection or other inflammatory lesion of the lungs. In 10 of the 55 cases which were studied, the infection of the lungs, insofar as could be ascertained, was primary. That is to say, it occurred without any preceding illness. In 13, the pneumonia was preceded by an infection of the upper respiratory tract and, in an additional 10, it was associated with pneumococcal infection. Other predisposing factors are listed in table 1.

Of considerable importance was the association of hemolytic streptococcal pneumonia with chronic processes in the lung, such as asthma, bronchiectasis, and chronic cystic disease of the lung. In these chronic infections, the acute pneumonia was caused by the hemolytic streptococcal infection and the underlying disease could be established only after the acute

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TABLE I

	Total Number of Cases	Empyema
1. Primary pneumonia.....	10	4
2. Upper respiratory infections, tonsillitis, scarlet fever	13	2
3. Associated pneumococcus infections.....	10	4
4. Chronic pulmonary infection.....	13	
Asthma.....	3	
Bronchiectasis.....	2	
Bronchitis.....	2	
Cystic disease.....	1	
Tuberculosis.....	1	1
Abscess.....	3	1
Pulmonary infarct.....	1	1
5. Bacteremia.....	1	1
6. Miscellaneous		
Associated heart disease.....	4	
Post-operative pneumonia.....	2	
Hemothorax.....		1
Mediastinitis.....		1

process had subsided. The presence of a chronic process in the lungs was also suggested from the history of the preceding illness in many cases.

Age. The cases were fairly evenly distributed throughout the second to the sixth decades, and only single cases were included in the first and eighth decades. Ten of the 16 cases of empyema were observed under 40 years of age. There was only one death under 30 years of age, whereas 6 of the 10 deaths occurred in patients over 40 years of age. The incidence of empyema was most striking under 30 years of age, although there were only three deaths in patients with empyema; one occurred under the age of one year and the other occurred in a man with a complicating heart disease (table 2).

TABLE II
Age Distribution With and Without Empyema

Age Groups	Total Cases	Empyema	Deaths
0-9	1	1 ¹	1
10-19	13	7	0
20-29	8	2	0
30-39	7	0	1
40-49	9	4 ²	2
50-59	10	0	1
60-69	6	1	5
70+	1	1	0
	55	16	10

White Blood Cell Counts. In those patients with pneumonia uncomplicated by empyema, the total white blood cell count varied between 7,000 and 59,000 per cu.mm. The average was between 10,000 and 30,000 per cu. mm. In the presence of empyema, the leukocyte count was usually higher since over half of the cases showed 40,000 or more cells. In the fatal

cases, the total leukocyte count was under 20,000 in all but one. In brief, it would appear that patients with empyema due to hemolytic streptococci are likely to show high leukocytosis (12,000 to 78,000). This is in striking contrast to the case reports¹ of hemolytic streptococcal pneumonia following epidemic influenza, in which the leukocyte count may fail to increase when pneumonia develops.

Bacteremia. The presence of hemolytic streptococci in the blood is always of serious prognostic significance although it is relatively infrequent in patients with hemolytic streptococcal pneumonia. Seven of the 55 patients showed bacteremia (12 per cent). Four of them died and the other three recovered, giving a fatality rate in the bacteremic cases of 57 per cent. This is in marked contrast to the fatality rate in the non-bacteremic cases, which was only 9 per cent. Of the bacteremic cases, only two were under 50 years of age. This suggests, of course, that the age of the patient influences the incidence of bacteremia in hemolytic streptococcal pneumonia just as it does in pneumococcal pneumonia.² With the exception of one patient who had empyema, which was secondary to a metastatic pneumonia, none of the patients with empyema showed bacteremia.

Specific Types in Pneumonia and Empyema. Through the courtesy of the Lederle Laboratories, Inc., who supplied us with serum, we were able to study the various specific types of hemolytic streptococci which were isolated. With the sera which were available, we were able to identify 32 of the 55 strains which were isolated from either the sputum, the blood, or the empyema fluid. They were distributed as follows.

TABLE III
Types of Hemolytic Streptococci Isolated in 55 Cases of Pneumonia and Empyema

Types	Pneumonia	Empyema
I.....	3	—
II.....	4	—
IV.....	1	—
XII.....	3	2
XIII.....	5	2
XV-XVII.....	15	5
XXVII.....	1	
Unidentified.....	23	7
Total.....	55	16

ANALYSIS OF VARIOUS GROUPS

Hemolytic Streptococcal Pneumonia Without Any Preceding Illness. In 10 cases, the pneumonia was not preceded by any illness and was considered to be a primary pneumonia. There was nothing distinctive about these cases. The onset was frequently abrupt with the symptoms of an acute infection and the local signs of pneumonia which were frequently diffuse in character and only rarely associated with frank signs of lobar con-

solidation. The etiologic diagnosis was made by examination of the sputum. In uncomplicated cases, the disease varied in duration from 7 to 21 days. There were two deaths in this group. One occurred in a woman 60 years of age who had bacteremia and a rapidly progressing illness of only seven days' duration. The other was a woman 66 years of age who had a prolonged illness of 49 days' duration and bacteremia on one occasion.

Hemolytic Streptococcal Pneumonia Preceded by an Acute Respiratory Infection or a Hemolytic Streptococcal Infection of the Throat. In a second group of 13 cases, the pneumonia was preceded by an acute upper respiratory infection, such as a common cold, pharyngitis, or tonsillitis. In these, the onset of the pneumonia was always associated with an increase in the severity of the symptoms. Examples of cases of pneumonia following tonsillitis and scarlet fever are illustrated in figures 1 and 2.

HEMOLYTIC STREPTOCOCCUS PNEUMONIA FOLLOWING TONSILLITIS

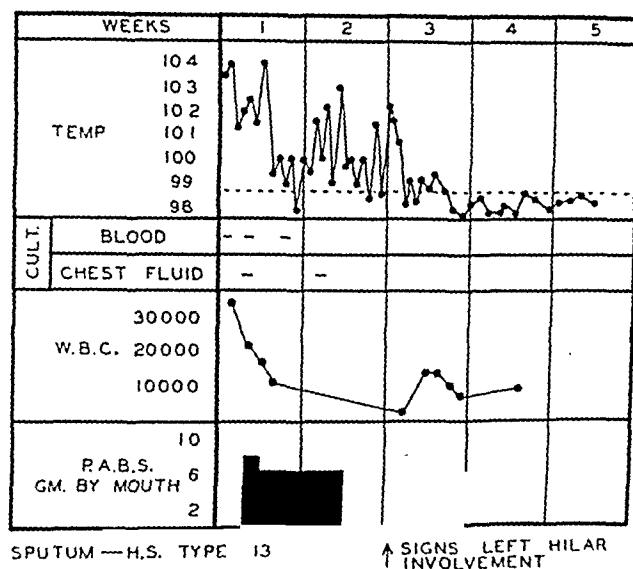


FIG. 1.

Hemolytic Streptococcal Pneumonia and Sterile Pleural Effusion Following Acute Tonsillitis.

Case 1. A young girl, 14 years of age, developed all the symptoms and signs of acute follicular tonsillitis one week before admission to the hospital. Three days after the onset of her illness she developed an acute pain in the right side of the chest, cough, and the expectoration of mucopurulent sputum. On examination, it was found that she had fever, leukocytosis, and the signs of a bronchopneumonia over the lower lobe of the right lung. The sputum contained numerous Type XIII hemolytic streptococci and the blood culture was negative.

Course of Illness. The course of the illness is charted in figure 1. The fever continued for 17 days. The blood cultures were always negative. On the third day of observation there were distinctive signs of a pleural effusion on the right side, and

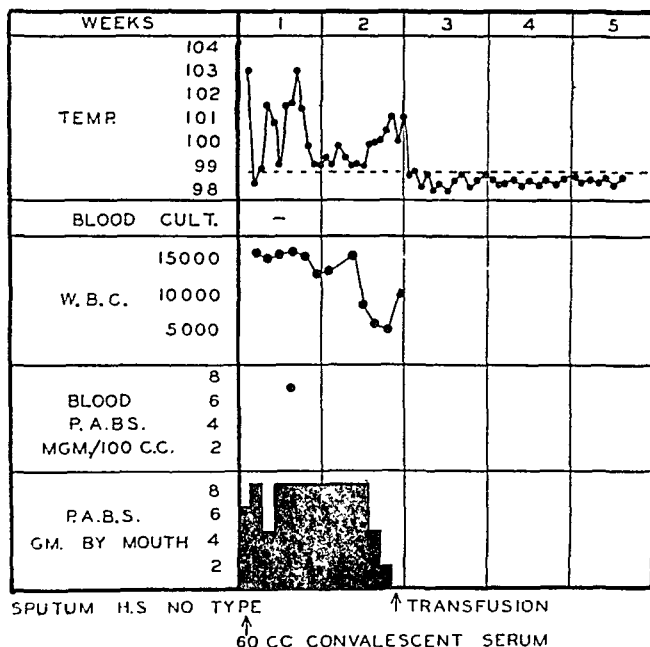
HEMOLYTIC STREPTOCOCCUS PNEUMONIA
FOLLOWING SCARLET FEVER

FIG. 2. P. A. B. S. Sulfanilamide.

200 cubic centimeters of hemorrhagic fluid were withdrawn from the chest. No organisms were found on either smear or culture. The chest was aspirated again on the eighth day of illness but the fluid continued to be sterile. After this aspiration the fluid disappeared. At first, there was high leukocytosis which decreased as the disease progressed. From the second to the eleventh day of her illness she received large amounts of sulfanilamide; then the drug was discontinued temporarily on account of nausea and vomiting and some improvement in her general condition. However, when it was discontinued, there was an increase in the fever and signs of a spreading process in the left lung appeared. Sulfanilamide was started again and continued for another six days, at which time the temperature had returned to normal.

Comment. There were several features of this case worthy of comment: first, the sterile effusion which disappeared after two aspirations without signs of purulent infection and, second, the exacerbation of fever and the spread of the process following the discontinuance of sulfanilamide. Both of these features stress the importance of continuing chemotherapy until all signs of active infection have disappeared.

Case 2. A woman, 34 years of age, developed scarlet fever at the end of a full term pregnancy. Two days after the onset of the sore throat she delivered a normal baby but continued to have fever varying from 100 to 104°. When she was seen in the hospital her temperature was 103°, the tonsils and throat showed the signs of an acute infection, and there was an eruption of the skin characteristic of scarlet fever. Two days later there were signs of pneumonia over the right lower lobe. The sputum contained many hemolytic streptococci and the blood culture was negative.

Course of Illness. This is shown in figure 2. On admission the patient was given 60 c.c. of anti-scarlatinal convalescent serum. This was followed by a prompt dis-

appearance of the rash and a striking decrease in the temperature. However, with the appearance of the signs of pneumonia, the temperature once again became elevated and continued for 14 days. Sulfanilamide was started on the day of admission and continued for 13 days, when it was stopped on account of a progressive anemia and a declining leukocyte count. She was given a blood transfusion on the fourteenth day and recovered completely.

Comment. This patient received convalescent serum for the toxic features of her infection and sulfanilamide for the local infection in the throat and lungs. It was also necessary to give her a blood transfusion for the progressive anemia. Her recovery was complete. This case serves to illustrate the importance of using antitoxic serum as well as chemotherapy in patients with scarlet fever complicated by a septic infection such as pneumonia.

In this group of cases there were no deaths. This was probably due to the fact that the patients were all under 40 years of age, none of them had bacteremia, and they were all treated promptly with sulfanilamide.

Hemolytic Streptococcal Pneumonia Following Bacteremia. In a previous study³ of 246 cases of hemolytic streptococcal bacteremia it was found that metastatic pneumonia occurred in 7.3 per cent of cases. Usually the fatality rate in these cases is exceedingly high unless active and energetic treatment is employed. Recovery may follow, however, when sulfanilamide is given in large amounts. The following case is an example.

Case 3. A young boy, 13 years of age, was admitted to the hospital complaining of pain in the right foot and ankle and high fever. He had been well until three days before admission when he became acutely ill with fever and great prostration. This was soon followed by pain, swelling, and redness in the right foot and ankle. Examination showed high fever, râles over the right lung posteriorly, and the signs of infection of the right ankle joint. The blood culture was positive for Type XIII hemolytic streptococci and there was leukocytosis.

Course of Illness. The fever and leukocytosis persisted for five weeks, and for 10 days there was bacteremia (figure 3). The signs of pneumonia increased over the right lung until signs were elicited over all three lobes. In the fourth week there were signs of a small empyema in the right pleural cavity and hemolytic streptococci were isolated from the pleural fluid on two occasions. The signs of an acute fibrinous pericarditis were present for three days during the fourth week of the illness. The patient was treated with large doses of sulfanilamide and multiple blood transfusions. The sulfanilamide was continued for 16 days until the blood was sterilized, and it was then discontinued temporarily because of the anemia which progressed in spite of the multiple blood transfusions. It was started for a second time when the empyema was discovered. After an illness of 10 weeks this young boy recovered completely.

Comment. The striking features of this case were: (1) the hemolytic streptococcal bacteremia without an obvious focus of entry; (2) the metastatic lesions in the ankle joint, lungs, pleura, and pericardium; (3) the complete recovery following sulfanilamide and multiple blood transfusions without the surgical drainage of the empyema.

One should note in this case, and it is true in most cases of hemolytic streptococcal sepsis, that the blood stream is not cleared promptly following

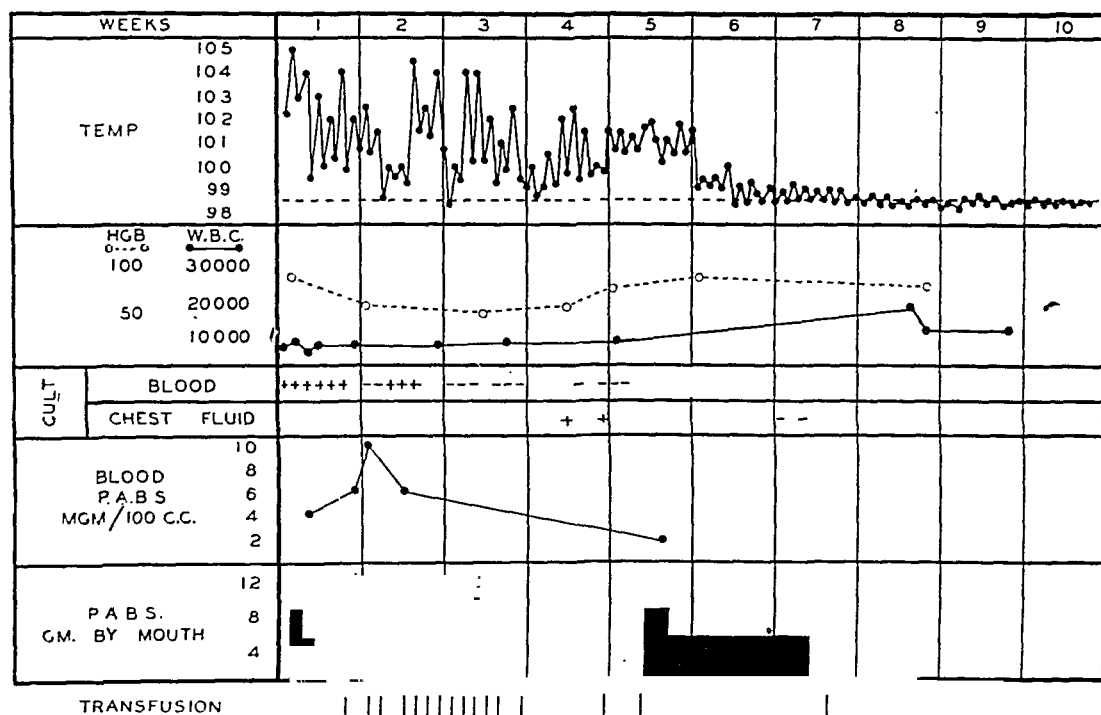
HEMOLYTIC STREPTOCOCCUS BACTEREMIA — PNEUMONIA AND EMPYEMA
RECOVERY WITHOUT OPERATION

FIG. 3. Chart illustrating the course of disease and treatment of hemolytic streptococcal bacteremia with pneumonia and empyema with sulfanilamide and multiple blood transfusions.

the use of sulfanilamide. Moreover, it was necessary to use multiple blood transfusions in order to prevent a rapidly progressive anemia. When these procedures are followed, recovery will follow in many cases. One should remember, however, that it is rare indeed to observe any dramatic or sudden change in the patient's condition following the use of sulfanilamide. The fact that they recover is impressive. Long-continued treatment is necessary for the best results.

Hemolytic Streptococcal Pneumonia Associated with Pneumococcal Infection. In 10 cases, the hemolytic streptococcus was associated with the pneumococcus as a cause of the pneumonia. The importance of mixed infections in the causation of pneumonia has been studied and reviewed recently by Finland⁴ who showed that most of the mixed infections were due to the pneumococcus and the hemolytic streptococcus. Cases of mixed infections have also been reported by Parsons and Myers⁵ and Solomon and Curphey.⁶ The types of pneumococci which were isolated along with the hemolytic streptococcus in our cases were Types I, III, VI, VIII, IX, XIX, and XI. In some cases, the hemolytic streptococcal infection was demonstrated when the pneumococcal infection was active. In others, the pneumococcal pneumonia was complicated by a hemolytic streptococcal abscess

of the lung, an empyema, or mediastinitis. In several instances, a relapse of the pneumonia or a reinfection of the lung was caused by the hemolytic streptococcus.

These cases of mixed infection comprise an important group since their course is often atypical, the complications are numerous, and the results of treatment may be difficult to interpret. Finland⁴ has shown that at least 6 per cent of all patients with pneumococcal pneumonia have evidence of a mixed infection of the lungs. He divided his cases into three groups: (1) those in which only one of the multiple organisms isolated from the sputum was responsible for the pulmonary infection; (2) those in which more than one organism had invaded the lung simultaneously, either at the same or different sites; and (3) those in which invasion by one organism followed the other. In these cases, with a relapse of infection, the same or different sites of the lung are involved. The cases which were reviewed by Solomon and Curphey⁵ probably belong in group 3, although it was not always possible to demonstrate a new focus in the lungs at the time of the hemolytic streptococcal bacteremia. In some, the bacteremia occurred following the recovery from the pneumococcal infection, and in others there were signs of delayed resolution of empyema. In any event, the sputum should be studied in all cases of pneumonia for evidence of a mixed infection and the blood should be cultured repeatedly in patients who have a protracted course and who are not responding to treatment.

Hemolytic Streptococcal Pneumonia in Patients with Chronic Pulmonary Disease. A common feature of chronic pulmonary disease is acute attacks of pneumonia. In 13 of the cases of hemolytic streptococcal infection, there was some chronic pulmonary disease preceding the attack of acute pneumonia. These cases included asthma, bronchiectasis, bronchitis, abscess of the lung, tuberculosis, and cystic disease of the lung. The diagnosis of the chronic disease of the lung was made from the history or from the condition of the lungs following recession of the acute process. There was one death in this group occurring in a 36 year old patient with bronchial asthma. All of the other patients recovered from their acute infection.

Usually, the course of events in these cases is as follows. A patient with a chronic pulmonary infection becomes acutely ill with high fever, prostration, and the signs of a diffuse pulmonary infection. The sputum is abundant and contains numerous hemolytic streptococci. After a period lasting from two to six weeks, the acute process gradually subsides, leaving the chronic process which may be quiescent or latent, or it may remain active. Not infrequently the process is repeated over a period of months. Each time hemolytic streptococci or other organisms may be isolated from the sputum.

Hemolytic Streptococcal Pneumonia in Miscellaneous Conditions. This group of six patients (table 1) illustrates the importance of chronic disease such as cardiac insufficiency in influencing the outcome of hemolytic strep-

tococcal pneumonia, since all four of the patients with heart disease and pneumonia died. Two had bacteremia and they were all 50 years of age or older. The other two cases in the group occurred following abdominal operations.

ANALYSIS OF FATAL CASES

There were 10 deaths in the 55 cases, or a gross fatality rate of 18.1 per cent. It was highest (57 per cent) in bacteremic cases and lowest in the non-bacteremic cases. Five of the patients had bacteremia and six were over 50 years of age. These points serve to stress the importance of age and bacteremia in influencing the outcome. One patient was only 10 months of age and had a complicating empyema.

The specific types of hemolytic streptococci which were present included Types I, II, XII, (XV-XVII). Death occurred within seven days after the onset of infection in four and between 21 and 48 days in the remaining five cases.

Factors which contributed to an unfavorable outcome were the presence of heart disease, asthma, and arteriosclerosis. There were three deaths among the patients with empyema, one in an infant 10 months of age, one in a patient with empyema following traumatic hemothorax, and a third in a patient with empyema associated with an infected infarct in heart disease.

The following is a list of the fatal cases.

1. Rapidly progressing infection with bacteremia in a woman 60 years of age.
2. Pneumonia in 5 patients with heart failure, aged 50, 60, 66, 60, and 34 years, respectively.
3. Multiple lobes involved in a woman 36 years of age with bronchial asthma.
4. Three patients with empyema.

From the study of this small group of cases, it would appear that age, bacteremia, complications, and associated debilitating diseases are important in prognosis.

EMPYEMA

Sixteen of the 55 patients had empyema, and death occurred in three. In 11, the empyema was associated with pneumonia. In seven, the pneumonia was due to the hemolytic streptococcus alone while, in four, there was an associated pneumococcal infection of the lung. The other causes for the empyema are listed in table 4.

The fatal cases occurred in a child 8½ months old, in the patient with the traumatic hemothorax, and in the man with the infected infarct of the lung.

Ten of the 16 cases occurred in patients under 30 years of age and, in general, it can be said that the incidence of empyema tends to follow the

TABLE IV

Empyema

(1) Streptococcal pneumonia.....	7
(2) Pneumococcal and streptococcal pneumonia.....	4
(3) Miscellaneous	
Tuberculosis of lung.....	1
Abscess of lung.....	1
Traumatic hemothorax.....	1
Mediastinitis following perforation of esophagus.....	1
Infected infarct.....	1
	<hr/> 16

frequency curve for hemolytic streptococcal pneumonia. It was most common under 20 years of age and over 40 years. Among the patients with hemolytic streptococcal infection of the lungs 13 (or 24 per cent) of the 53 developed empyema. It was most frequent in patients who had pneumonia without any preceding chronic pulmonary infection. In this group of 34 cases, there were 11 with empyema or 32 per cent.

The empyema usually occurred during the active stage of the pneumonia and, with the exception of the patients who had only a small amount of purulent fluid in the pleural cavity, the course was protracted and lasted from 6 to 14 weeks or longer.

Once the signs of empyema developed, the features of a septic infection were conspicuous; that is, irregular fever, high leukocytosis, a progressive anemia, and loss of weight. In those who had a thoracotomy with drainage of large amounts of fluid from the chest, malnutrition and hypoproteinemia were occasionally seen.

Treatment of Empyema. For purposes of discussion, the cases are divided into two groups: (1) those recovering without thoracotomy and (2) those recovering following operation. All of the patients received either sulfanilamide or sulfapyridine.

Patients Recovering Without Thoracotomy. There were four patients in this group. They were all treated with chemotherapy and aspiration of the chest. In two, the amount of purulent fluid was small and did not exceed 15 c.c. with each aspiration. In the remaining two, the amount of fluid aspirated each day varied between 150 and 300 c.c.

The following case illustrated the course of events in a patient recovering without thoracotomy.

Case 4. A young man suddenly became ill with the symptoms and signs of pneumonia involving the left lower lobe of the lung. There was high fever and leukocytosis. The blood culture was negative. On the third day of his illness signs of fluid appeared over the left lower lobe and aspiration of the pleural cavity disclosed 500 c.c. of thin, serous exudate containing Type XV/XVII hemolytic streptococci. The chest was tapped daily for 5 days and, in all, 1050 c.c. of fluid were removed. Organisms were isolated from the fluid on the first four days but on the fifth day the fluid was sterile. He recovered completely and was discharged from the hospital 6 weeks after admission. From the first day of his illness and for a period of 11 days, he received 4 grams of sulfapyridine a day, a total of 44 grams. Three days after the pleural fluid became sterile, the drug was discontinued.

Comment. This case is an example of recovery following repeated aspirations of the pleural cavity and chemotherapy. The interesting feature is that the fluid was sterilized within five days of the beginning of treatment and while the pneumonia was still active.

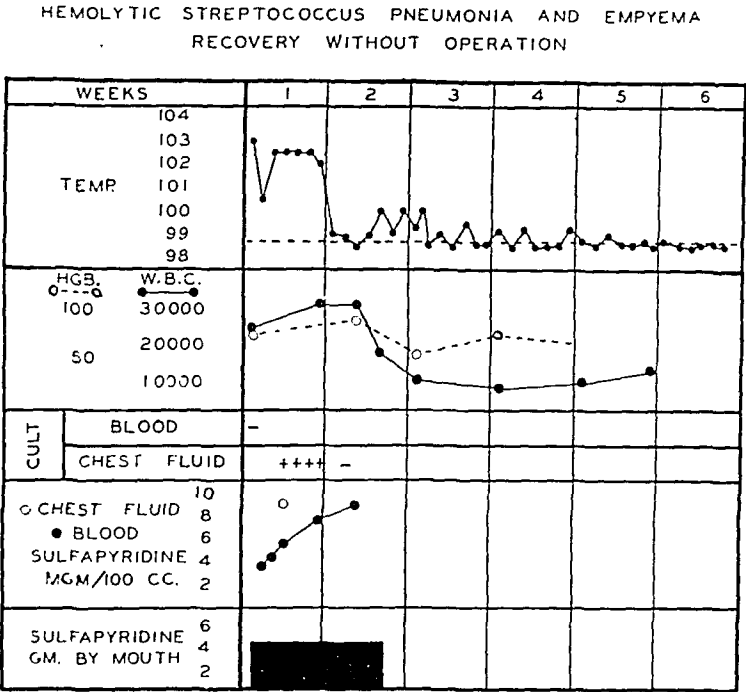


FIG. 4.

The following case illustrates the recovery of pneumonia and empyema following aspiration of the chest and chemotherapy. It also illustrates the fact that acute rheumatic fever will occur following hemolytic streptococcal infection in spite of energetic and active chemotherapy.

Case 5. A young boy, 15 years of age, had been ill with the symptoms and signs of pneumonia for five days before admission. When he was seen on the sixth day of his illness he had fever, leukocytosis, and the signs of pneumonia over the left lower lobe. The sputum contained many hemolytic streptococci which could not be typed with the sera that were available. The blood culture was negative. Two days after admission there were signs of fluid in the left pleural cavity and, when a needle was inserted into the chest, 7 c.c. of fluid containing many hemolytic streptococci were withdrawn. Sulfanilamide was started and continued in large amounts for five weeks.

Cases of Empyema Recovering Following Thoracotomy. There were nine patients with empyema who recovered following chemotherapy and thoracotomy. These cases were of special interest since all of them received sulfanilamide prior to operation in an attempt to sterilize the empyema. A number of facts emerged from the study of these cases which aid greatly in the management of cases of empyema when chemotherapy is used. These points can be illustrated by several cases.

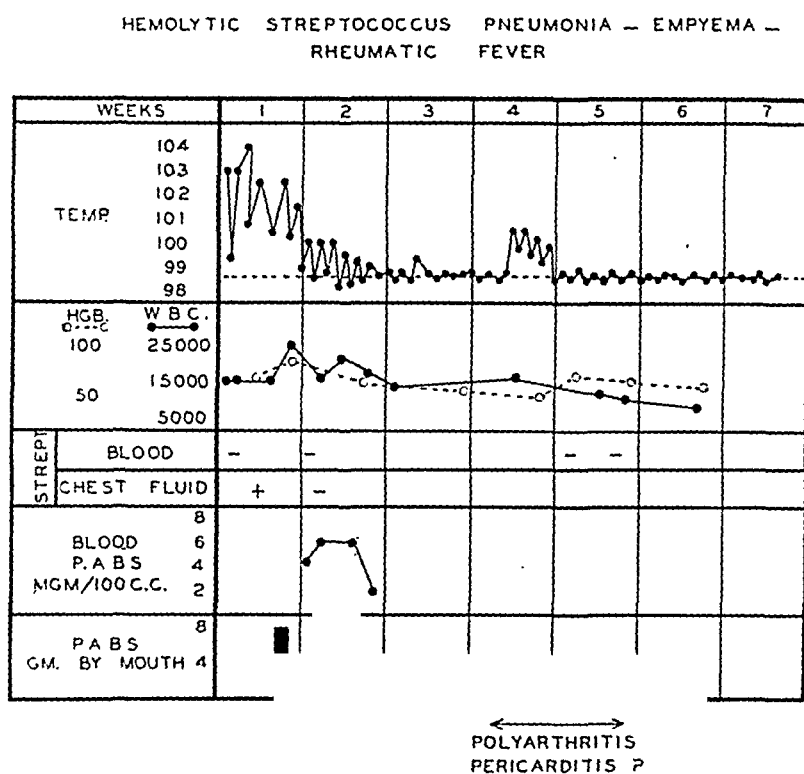


FIG. 5.

Case 6. A girl, aged 15 years, with hemolytic streptococcal pneumonia and empyema recovers temporarily following aspiration of the chest and chemotherapy. Complete recovery follows thoracotomy.

A young girl, 15 years of age, was ill for six days with fever and sore throat before admission to the hospital. She had fever, leukocytosis, the signs of pneumonia over the lower lobe of the right lung, and Type XV/XVII hemolytic streptococci in the sputum. The blood culture was negative. On the seventh day after admission there were signs of fluid in the chest in spite of the fact that the temperature was lower. The chest was tapped on the eighth day of the illness and 2000 c.c. of thin, serous fluid containing hemolytic streptococci were removed. This was repeated on five occasions during a two-week period, and a total of 3150 c.c. of fluid were aspirated from the chest. During this period she was given large amounts of sulfanilamide and four blood transfusions. The temperature remained normal for three weeks and she was discharged home for two weeks but she again returned to the hospital with high fever and the physical signs of a recurrence of the empyema. The blood cultures were negative. The chest was again tapped and a small amount of infected fluid removed. Sulfanilamide was started once again but, in spite of a temporary decrease in temperature, the pleural fluid continued to be infected and reaccumulated. Recovery followed thoracotomy. The course of the illness is shown in figure 6.

Comment. In this case there was a temporary recovery from an empyema following multiple aspiration of the chest and chemotherapy. Indeed, the results were so striking that the patient was allowed to return to her home. After a period of five weeks, there was a recurrence of symptoms and signs of empyema and recovery occurred only after free drainage of fluid

was obtained. It is well, therefore, to follow all patients for a considerable period of time following chemotherapy and aspiration of the chest since there may be a recurrence of infection in spite of a temporary disappearance of all signs of active infection.

The following case illustrates how chronic the course of a hemolytic streptococcal empyema may be in spite of chemotherapy, drainage of the empyema cavity, and thoracotomy.

HEMOLYTIC STREPTOCOCCUS PNEUMONIA — EMPYEMA
RECOVERY FOLLOWING OPERATION

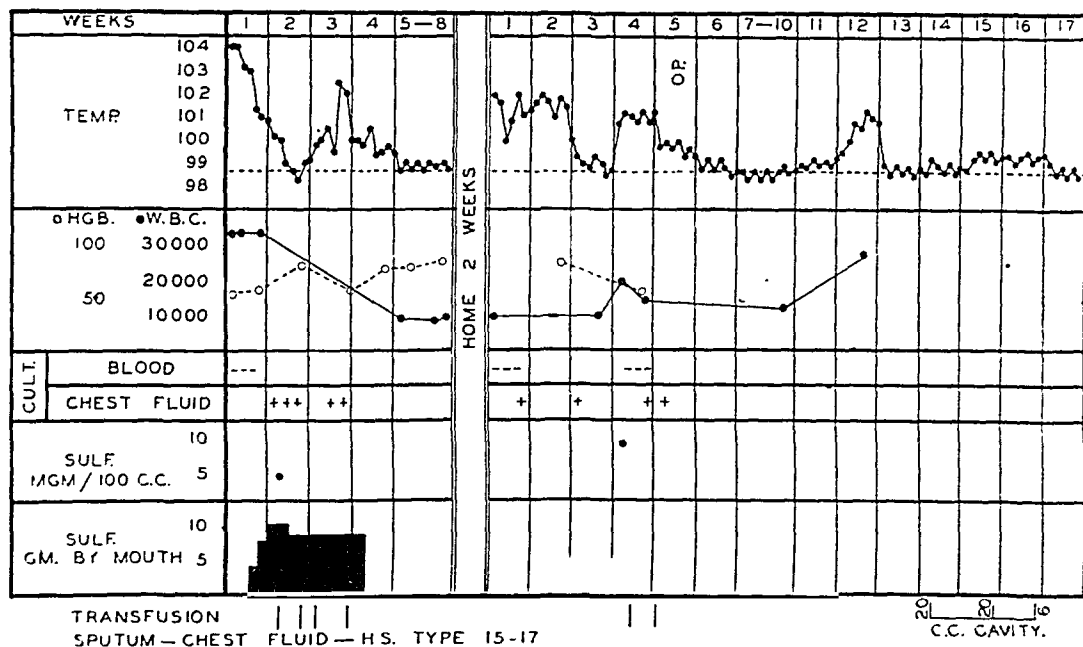


FIG. 6.

Case 7. A boy, 15 years of age, was admitted to the hospital during the first week of an acute illness. At the time of admission he was found to have the signs of pneumonia and empyema of the left lung and pleura, respectively. The sputum contained Type XII hemolytic streptococci. The blood cultures were negative but the fluid aspirated from the left pleural cavity contained many Type XII hemolytic streptococci. He was acutely ill and, during the first seven days of observation, 3000 c.c. of thin, serous fluid were aspirated from the left chest. On the eighth day a closed thoracotomy was done but, since there was very little improvement and inadequate drainage, a rib resection was done on the fourteenth day of his illness. He was given multiple blood transfusions for a progressive anemia and the pleural cavity was irrigated with sulfanilamide in a concentration of 20 mg. per 100 c.c. There was gradual but progressive improvement for nine weeks when he was discharged from the hospital. He remained at home for eight weeks and then returned on account of fever and pain in his chest. It was found that he had a recurrence of a small empyema at the site of the original infection. The cavity was opened, chemotherapy was started again, and he recovered promptly. These episodes were repeated on three different occasions until 10 months after the onset of his illness when it was found that he had a sinus leading from the chest wall into a small cavity and there was a *Staphylococcus*

aureus infection. Following excision of the sinus and establishment of free drainage he finally recovered completely. The clinical course is illustrated in figure 7.

Comment. In spite of large amounts of sulfanilamide and multiple aspirations of the chest, it was not possible to influence the course of this boy's illness in a favorable sense until a thoracotomy was done. Even then, he had several recurrences of the local infection. This case, then, is an example of the chronic character of some cases of hemolytic streptococcal empyema, and it also serves to emphasize the fact that all available forms of treatment must be used in order to effect a cure.

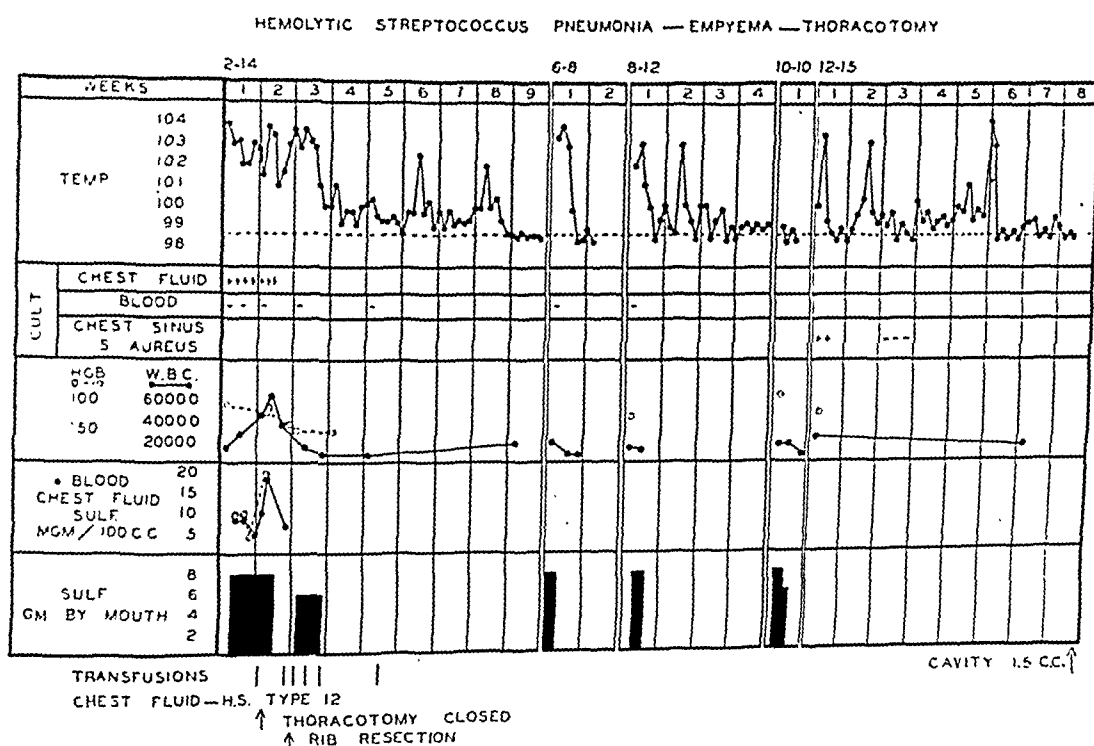


FIG. 7.

The next case demonstrates that the fluid in the pleural cavity may be sterilized temporarily following repeated aspirations of the chest and chemotherapy but, once it is discontinued, the infection may recur so that surgical operation is necessary.

Case 8. A boy, 13 years of age, became ill with the symptoms and signs of pneumonia. Within two days after admission to the hospital there were signs of a left-sided pleural effusion. There were high fever, leukocytosis, and negative blood cultures. The sputum contained many Type XII hemolytic streptococci. The pleural fluid was thin and serous and contained many Type XII hemolytic streptococci. During the first two weeks of observation the pleural cavity was tapped three times and 1630 c.c. of infected fluid were withdrawn. Sulfanilamide was given by mouth for 10 days and was discontinued on account of an anemia. Three blood transfusions were given, as indicated in figure 8, for the anemia and to replace plasma protein

which was being lost from the multiple aspirations of the chest. The patient had developed moderate edema of the ankles and the plasma proteins were 6.1 grams per 100 c.c.

During the third week, the temperature ranged between 99 and 99.5° and 250 c.c. of fluid aspirated from the chest were sterile. This was somewhat misleading inasmuch as the patient continued to have low-grade fever. Finally, during the sixth week, 55 c.c. of fluid were again withdrawn and proved to be infected. A thoracotomy was performed and free drainage was established. He recovered gradually and, with the exception of an intercurrent respiratory infection during the eleventh week, he recovered completely. The course of his illness has been charted in figure 8.

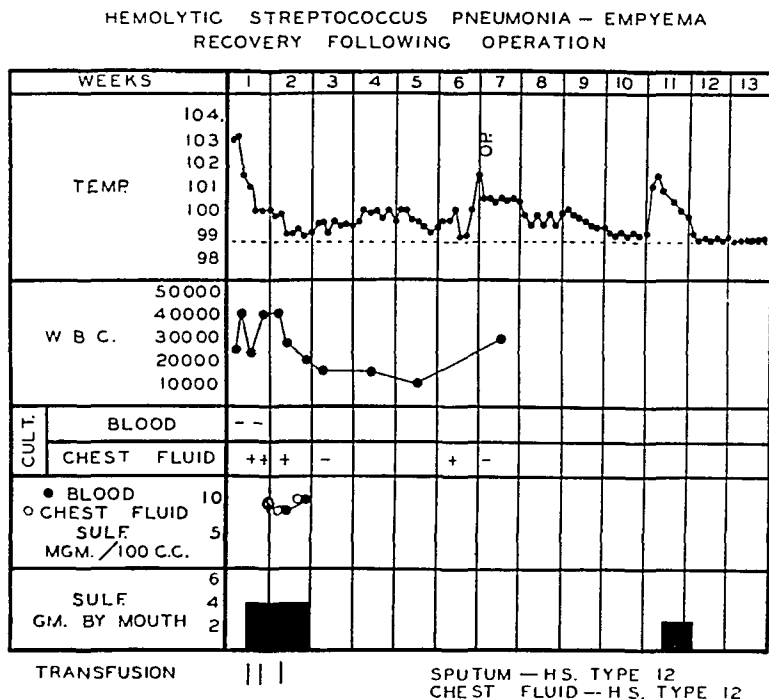


FIG. 8.

Comment. In this case, the pleural fluid was sterilized temporarily following sulfanilamide and aspiration of the pleural cavity, but complete recovery followed the establishment of free drainage of the empyema cavity. One should not be deceived by the temporary sterilization of the fluid in these cases since, on a number of occasions, we have observed that this temporary improvement has been followed by a reinfection of the fluid and recovery only follows surgical treatment.

COMMENT

From our own studies and those of others, it seems plain that the hemolytic streptococcus is a frequent secondary invader in the lung. It infects the lung following measles, epidemic influenza, the common cold, sore throat, or erysipelas. Occasionally it acts as a secondary invader in pneumococcal

pneumonia, and not infrequently metastatic pneumonia due to this organism occurs in patients with streptococcal bacteremia. Bronchiectatic abscess cavities as well as cysts of the lung are infected frequently with streptococci, and sterile pleural effusions following lung tumors, or pulmonary infarcts may become infected.

Characteristically, the hemolytic streptococcus produces an interstitial or confluent bronchopneumonia. It is followed by empyema in a high percentage (20 per cent) of cases, and suppurative lesions of the lungs (bronchiectasis and lung abscess) are not uncommon. Mediastinitis, pericarditis, and suppuration of the subcostal lymph nodes are not infrequent lesions in the fatal cases. Bacteremia occurs in only about 10 to 15 per cent of cases and, commonly, as a late event in the course of the disease.

The fatality rate has been reported as varying between 30 and 60 per cent of cases. In our small group of 39 patients with pneumonia, it was only 17 per cent. Unfavorable factors in the course of the disease were age, bacteremia, and the presence of some chronic illness such as heart disease. The outcome will also depend upon the treatment employed and this will be commented upon presently.

The treatment of hemolytic streptococcal pneumonia prior to the widespread use of the sulfonamide group of drugs was largely supportive and symptomatic. Amoss and Craven⁷ reported encouraging results from the use of anti-streptococcic serum in 1930, but this form of treatment has never received widespread use. The reason for this is the difficulty in typing hemolytic streptococci and in producing potent antibacterial as well as anti-toxic serum.

With the introduction of the sulfonamide drugs, a new group of therapeutic agents has been used with some success. It is difficult even now to make any remarks which can be considered to be final in respect to the efficiency of these drugs in the treatment of pneumonia due to this organism since there are so many variable factors in assessing the value of treatment in this disease. A few facts of significance have emerged; namely, sulfanilamide does not produce any dramatic change in the course of hemolytic streptococcal pneumonia, and it does not seem to reduce the incidence of empyema. It is perhaps significant that there was only one death in 28 patients between the ages of 10 and 40 years, and in this group there were nine cases of empyema. Moreover, in the 16 patients with empyema, there were only three deaths and, in all, there were other unfavorable factors which influenced the outcome of the disease, such as age (one patient was less than one year of age), heart disease, and traumatic hemothorax. It would appear, therefore, that sulfanilamide will influence the outcome of hemolytic streptococcal pneumonia and empyema in that it will reduce the fatality rate.

In a recent study of 78 cases of hemolytic streptococcal empyema by Nowak,⁸ the fatality rate in patients who did not receive sulfanilamide was

48 per cent, whereas in those who received it, the fatality rate was 29 per cent. Leahy⁹ of Buffalo has also reported his observations in seven cases of hemolytic streptococcal empyema treated with sulfanilamide, aspiration of the chest, or open thoracotomy with only one death. With the exception of one patient, who was 20 years of age, all of his patients were under 10 years of age. Bacteremia was present in one. Sulfanilamide and multiple aspiration of the pleural cavity were used in four cases, all recovering. Sulfanilamide and rib resection were employed in one with recovery, and sulfanilamide and closed drainage in two resulted in one death. From these cases, it would appear that in some young patients multiple aspirations and sulfanilamide will be sufficient. In others, closed or open drainage will also be required. It is well to recall that surgeons of wide experience report recovery from hemolytic streptococcal empyema in about 10 to 15 per cent of cases following multiple aspirations.¹⁰ It may be possible, especially when the pleural effusion is small, to increase the number of recoveries by this method without rib resection with the use of sulfanilamide or the other compounds.

Our experience so far, however, would indicate that even when sulfanilamide is used, open drainage of the pleural cavity will be required in most cases. One must not be misled or deceived by the temporary sterilization of the empyema cavity since we have observed recurrences of infection as long as three to five weeks after such an event. It is possible that treatment with sulfanilamide for a longer period of time after the fluid has been sterilized will increase the number of cures by this method. However, in our experience thus far, one must be guarded.

Aside from the use of chemotherapy and surgical treatment of empyema, other measures are of the greatest importance in the treatment of the patient. They all develop a progressive anemia which is accentuated by the sulfanilamide. For this reason, many of these patients are improved by using blood transfusions. Also, when large amounts of plasma protein are being removed from the chest, malnutrition and a plasma protein deficit may develop. This complication is treated most adequately by means of increasing the food intake and blood transfusions.

One may sum up the experience so far by saying that intensive chemotherapy reduces the fatality rate in hemolytic streptococcal pneumonia and empyema. It may also sterilize the pleural infection following multiple aspirations in some cases. In most instances, however, it neither shortens the course of the disease nor prevents the incidence of empyema. Chemotherapy, when used along with other forms of treatment, is of considerable value in the treatment of these infections.

SUMMARY AND CONCLUSIONS

1. Fifty-five cases of hemolytic streptococcal pneumonia and empyema have been studied and analyzed with respect to outcome and treatment, and

illustrative cases are presented. There were 39 cases of pneumonia alone and 16 cases of empyema. Fourteen of the 16 cases of empyema followed an infection of the lung.

2. The cases of pneumonia could be divided into three groups: (1) those which were primary; (2) those which followed a respiratory infection; and (3) those which were superimposed on a preëxisting chronic pulmonary infection.

3. The fatality rate in the 39 cases with pneumonia was 17 per cent. Unfavorable factors in influencing the outcome were age (i.e. over 50 years), bacteremia, and debilitating disease. The fatality rate in patients with empyema was 18 per cent, but it was striking that there was only one death from empyema between the ages of 10 and 40 years.

4. Bacteremia was present in 12 per cent of cases. It was more common in the patients over 50 years of age, and the fatality rate in bacteremic cases was 57 per cent, whereas in the non-bacteremic cases it was only 7 per cent.

5. The use of sulfanilamide or sulfapyridine did not reduce the incidence of empyema, and it was not possible to show that it shortened the course of the disease. There was suggestive evidence that the fatality rate in both the cases of pneumonia and empyema was reduced by using these drugs.

6. There were four cases of empyema which recovered following multiple aspirations of the chest and chemotherapy. The best results were obtained with a combination of chemotherapy and thoracotomy.

REFERENCES

1. MACCALLUM, W. G.: The pathology of the pneumonia in the United States Army Camps during the winter 1917-1918, Monograph 10, Rockefeller Institute for Medical Research, 1919.
2. TILGHMAN, R. C., and FINLAND, M.: Clinical significance of bacteremia in pneumococcic pneumonia, *Arch. Int. Med.*, 1937, lix, 602.
3. KEEFER, C. S., INGELFINGER, F. J., and SPINK, W. W.: Significance of hemolytic streptococcic bacteremia. A study of two hundred and forty-six patients, *Arch. Int. Med.*, 1937, lx, 1084.
4. FINLAND, M.: The significance of mixed infections in pneumococcic pneumonia, *Jr. Am. Med. Assoc.*, 1934, ciii, 1681.
5. PARSONS, J. W., and MYERS, W. K.: Streptococcic sepsis complicating recovery from pneumococcic pneumonia, *Jr. Am. Med. Assoc.*, 1933, c, 1857.
6. SOLOMON, S., and CURPHEY, T. J.: Streptococcic septicemia complicating pneumococcic lobar pneumonia, *Jr. Am. Med. Assoc.*, 1940, cviii, 187.
7. AMOSS, H. L., and CRAVEN, E. B., JR.: Serum treatment of hemolytic streptococcus pneumonia, *Jr. Clin. Invest.*, 1933, xii, 885.
8. NOWAK, S. J. G.: Empyema thoracis: an analytical study of 500 cases with general remarks, *Med. Clin. N. Am.*, 1939, xxiii, 1355.
9. LEAHY, L. J.: The use of sulfanilamide in the treatment of hemolytic streptococcic empyema, *N. Y. State Jr. Med.*, 1930, xl, 347.
10. GRAHAM, E. A., SINGER, J. J., and BALLON, H. C.: Surgical diseases of the chest, 1935, Lea & Febiger, Philadelphia, p. 138.

CEREBRAL MANIFESTATIONS OF BACTERIAL ENDOCARDITIS*

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EMBOLIC lesions of the brain and cerebral vessels are as integral a part of bacterial endocarditis as are the embolic lesions of other structures, and the resulting neurological symptoms and signs merit equal importance with the café-au-lait coloring, clubbed fingers, enlarged spleen and conjunctival petechiae in the symptomatology of the syndrome.

Two cases recently seen on the wards of the Hospital Division of the Medical College of Virginia would have proved to be less puzzling diagnostic problems had this been realized. The first case was a colored male (Case 1) with a purulent meningitis, clubbed fingers and an enlarged heart without murmurs who was found to have a large vegetation on the aortic cusp at autopsy. The second case was admitted to the hospital, irrational and with a stiff neck (Case 2). Purulent spinal fluid containing blood was obtained on lumbar puncture. An aortic diastolic murmur was noted on examination, but the cardiac pathology was thought to be incidental until the spleen became palpable several days later and the fingers began to show early clubbing. With these two cases in mind, it was decided to survey the records of patients with bacterial endocarditis admitted over a period of several years and determine the frequency of occurrence and the types of cerebral lesions present in these.

Between June 1, 1932, and December 31, 1938, 35 patients with bacterial endocarditis were seen in the Hospital Division of the Medical College of Virginia. Seventeen (48.5 per cent) of these cases presented some type of cerebral sign or symptom and were selected for detailed study. Nine cases were admitted to the hospital primarily as neurological, neurosurgical or mental patients and made up 25 per cent of the total number of the 35 cases examined. Many of these patients were referred to the hospital for reasons quite foreign to the real issue, and some followed devious channels before being successfully diagnosed and arranged on the proper service. One was referred as a right frontal lobe tumor; another came from a distance of approximately 500 miles for the repair of an old skull fracture; a third came for psychiatric observation because he was accusing his fellow prisoners of poisoning his food and drink. Still another was rushed in by excited friends after the occurrence of a convulsive seizure, and a fifth patient descended on an unsuspecting house staff with a left hemiplegia and aphonia.

Meningitis, hemiplegia, subarachnoid hemorrhage and other neurological disturbances were noted from the very early descriptions of the disease.

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Osler¹ made several distinct references to such occurrences. More detailed studies, however, have for the most part been confined to the pathologic or purely neurological aspects. Kimmelstiel,² in 1927, made a thorough pathologic investigation of the brain lesions of subacute bacterial endocarditis in which he found inflammatory changes in the brain in 10 out of 13 cases. The outstanding, and most characteristic, change noted by this writer was a diffuse embolic encephalitis showing no predilection for any single portion of the brain substance. Microscopically the changes were characterized by glial proliferation, polymorphonuclear cell infiltrations with actual abscess formation in many instances, monocytic meningitis, ependymitis and inflammatory changes in the blood vessel walls. Less frequently did he note localized areas of ischemia and softening, degenerative changes in vascular structures and areas of hemorrhage into the brain substance. Diamond³ in a detailed pathologic report noted similar changes and called especial attention to the formation of nodules of glial and mesodermal tissue, abscesses, degenerative areas, and inflammatory and degenerative changes in the blood vessel walls. De Jong⁴ noted emboli and thrombi in cerebral vessels, subarachnoid and intraventricular hemorrhage, meningitis, brain abscess, and mycotic aneurysms. In his study of 68 cases, 17 presented clinical or pathologic evidence of central nervous system disease and six were admitted to the hospital on this account. Libman⁵ noted the occurrence of cerebral emboli in 27 of 59 cases of subacute bacterial endocarditis and observed such symptoms as vertigo, headache, irritability, insomnia, delirium, stupor and coma in many of these cases. Winkelmann⁶ in his description of the pathologic changes in 13 cases of bacterial endocarditis noted such conditions as meningitis, toxic endarteritis, organized emboli with degenerative brain changes, multiple abscesses and mycotic aneurysms. Lereboullet and Mouzon,⁷ Smith and Brumfiel,⁸ Tice,⁹ Ullom,¹⁰ Cabot,¹¹ Denman¹² and others¹³⁻²⁷ have reported cases of bacterial endocarditis with cerebral or other central nervous system manifestations.

CASE REPORTS

Case 1. R. C., colored male, aged 42. Three and a half weeks before admission to the hospital the patient developed a severe cold and had to stop work. Shortly after this he developed a protracted cough which was productive of a thick, purulent sputum. Examined at this time by his family physician, he was told that he had some type of lung trouble and he was referred to the local tuberculosis sanatorium for further examination, and from there to St. Philip Hospital. The productive cough continued unchanged in character and, in addition, he developed a pain in his right chest which had been present for about three days before hospitalization. Inventory by symptoms and past history were non-contributory.

Physical examination: Temperature 101.6° F., pulse 90, respiration 22, blood pressure 110 mm. of mercury systolic and 70 diastolic. The patient was a well developed, well nourished colored male, lying quietly flat in bed, rational, alert, and co-operative. To general appearances he did not seem acutely ill. The head and neck were negative except for the presence of impacted wax in both auditory canals. There

was a prolongation of the expiratory phase over the right apex, but no definite evidence of pathologic change. The heart sounds were faint and distant, and the apex beat could not be visualized or palpated; nor could the left border be outlined by percussion. There were no murmurs. Abdominal examination was negative. A marked clubbing of the fingers and toes was present. All tendon reflexes were hypo-active; no pathological reflexes were noted.

Laboratory data: *urine*, amber, alkaline, specific gravity 1.032; albumin, sugar and acetone negative; sediment negative. *Blood*: 4,000,000 red blood cells; 78 per cent hemoglobin; 14,400 white blood cells; 88 per cent polymorphonuclear cells, 8 per cent lymphocytes, 4 per cent monocytes. Wassermann and Kline reactions were negative. *Blood culture*: 9-10-37, 9-11-37 and 9-13-37, pneumococcus type IV (group B). *Electrocardiogram*: 9-11-37, negative except for sinus tachycardia.

On 9-6-37 it was noted that the patient had a definite stiffness of the neck. A lumbar puncture was done, revealing a cloudy spinal fluid under 175 mm. of water pressure, containing 1,200 white blood cells, 96 per cent polymorphonuclear cells, 4 per cent lymphocytes; sugar 30 mg., globulin heavy trace, Wassermann and mastic negative. Smear and culture were negative. The patient was placed on sulfanilamide therapy both orally and intraspinally, but failed to respond to any appreciable degree. On 9-11-37 the following note was made: "The heart is enlarged to the left as indicated by the apex which is well to the left of the mid clavicular line; all second sounds are diminished in intensity, no murmurs are heard, the spleen is not palpated, the pulse is typically dicrotic and the fingers clubbed." Repeated lumbar punctures showed an elevated pressure with a white blood cell count which dropped from 1,200 on 9-6-37 to 145 on 9-12-37. The polymorphonuclear cell differential count was always in excess of 85 per cent. Repeated smears and cultures on this fluid were negative for any type of organism. The patient died on 9-19-37, 16 days after admission to the hospital.

Clinical diagnosis:

1. Septicemia, pneumococcic.
2. Meningitis, acute.
3. Chronic bronchitis.

Postmortem examination:

Autopsy diagnosis: Old healed endocarditis of aortic cusps and mitral valve; globular ulcerative endocarditis of aortic cusps and mitral valve; cardiac dilatation and hypertrophy; septic infarcts of kidney and spleen (spleen weight 200 gm.); broncho-pneumonia, right lower lobe; caseation of hilar nodes, left.

Brain: The meninges covering the convexity of the brain were smooth, moist and glistening. At its basal portion, however, there was creamy pus in the subarachnoid space. Coronal sections revealed small hemorrhages 3 mm. in diameter at the border of the white and gray matter. The right occipital lobe showed multiple areas of softening which were well demarcated and rather large.

Histological examination: Various changes of inflammatory and degenerative nature were found throughout most of the brain sections. They were most marked in the pons, thalamus, posterior portion of the lenticular nucleus and in the occipital lobe. The following types were noted: 1. Small discrete nodules of glial proliferation intermixed with scattered polys and monocytes; in the center of one of these foci was a large mononuclear cell filled with diplococci. 2. Larger and more ill-defined foci of necrosis with large protoplasmic glial cells and hazy matrix with nuclear fragments and a few polymorphonuclear leukocytes. 3. Small abscesses. 4. Ill-defined foci of degeneration with crowded ganglion cells which undergo various types of degeneration and show evidence of neurophagia. 5. Perivascular infiltrations were found in various areas consisting of lymphocytes, monocytes and poly-

morphonuclear cells. 6. Rather marked meningitis was noticed which was of mixed nature, consisting of polymorphonuclear cells and monocytes. 7. A large area of softening in the occipital lobe which was characterized by loss of normal structure, accumulation of foam cells and crowding of numerous new formed capillaries with swollen endothelial cells. The greater part of the area of softening does not contain polymorphonuclear cell infiltration.

Final diagnosis:

1. Healed endocarditis of the aortic cusps and mitral valve.
2. Bacterial endocarditis, acute—pneumococcic.
3. Bronchopneumonia.
4. Meningo-encephalitis, embolic.

Case 2. L. M., colored female, aged 20. Until three weeks before admission to the hospital this patient was in excellent general health. At this time she first noticed a rather pronounced loss of appetite and a peculiar ringing sound in her ears which she described as sounding as if someone was "unwrapping packages." One week later she developed a severe generalized headache which was associated with a dizzy, unsteady sensation. These symptoms continued unchanged until the day before admission when she developed pain and a stinging sensation in both eyes, and shortly after this it was noticed that she could not see out of the right eye.

Physical examination: Temperature 103°, pulse 104, respiration 20, blood pressure 115 mm. of mercury systolic and 25 diastolic. The general appearance was that of an acutely ill, semistuporous person, lying flat in bed with eyes closed. She could be aroused to answer simple questions but then lapsed into a state of lethargy. The right conjunctiva showed a marked hyperemia with engorgement of the superficial vessels and swelling of both lids. The fundi were negative. The neck was stiff and attempts at anterior posterior flexion were accompanied by exquisite pain. No pathologic change was noted on examination of the chest and lungs. The apex beat was palpated in the fifth intercostal space almost in the anterior axillary line; no thrills were present. A systolic murmur was heard over the apex and a diastolic murmur over the aortic area. The pulmonic second sound was accentuated, and the pulse was of a collapsing type. The liver edge was palpated 2 cm. below the costal margin. On examining the extremities and reflexes, no contributory factors were noted.

Laboratory data: *Urine*: negative for blood and albumin. *Blood*: hemoglobin 60 per cent; white blood cells 25,300. *Serology*: Kline and Wassermann tests positive. *Blood culture*: positive for *Streptococcus hemolyticus*. *Spinal fluid*: white blood cells 403; polymorphonuclear cells 88 per cent; lymphocytes 12 per cent; red blood cells 1,650; culture positive for *Streptococcus hemolyticus* (third specimen).

On account of the stiff neck and febrile state, the case was thought at first to be one of meningitis, and a spinal puncture was done immediately. The fluid obtained was cloudy and under pressure. Sulfanilamide therapy was begun at once. There was no appreciable change, however, and on 10-30-37 an enlarged spleen and early clubbing of the fingers were noted, and the diagnosis of acute bacterial endocarditis with meningitis was substituted.

Clinical diagnosis:

1. Luetic heart disease.
2. Aortic regurgitation.
3. Acute bacterial endocarditis.
4. Meningitis, acute (*Streptococcus hemolyticus*).

Postmortem examination:

Autopsy diagnosis: Old healed endocarditis of the mitral valve with fresh superimposed globular vegetations; acute diffuse myocarditis and focal beginning abscesses;

large soft spleen (weight 320 grams); acute focal interstitial pneumonitis; embolic suppurative nephritis.

Brain: In gross showed slight injection of the vessels of the right cerebral hemisphere with a small subarachnoid hemorrhage over the base of the right temporal lobe. Coronal section revealed a rather large hemorrhage in the left collateral fissure measuring 4 by 1 by 1 cm. in diameter. There was a small cystic area in the left hemisphere just above the internal capsule.

Histological examination: 1. A large abscess was present in the white matter of the parietal lobe with complete liquefaction of the center containing masses of bacteria. 2. Foci of necrosis with very hazy matrix containing debris and some fibers surrounded by a wall of glial cells. These foci did not contain, or contained only a few, polymorphonuclear cells. 3. Many discrete nodules of glial proliferation which are rich in nuclei. 4. Irregularly distributed perivascular infiltration with round cells, monocytes and polymorphonuclear cells. 5. Meningitis was present in various areas, mononuclear in some instances and of a polymorphonuclear character in others. 6. Degenerative changes of ganglion cells were noticed in many areas. There was homogenization of the cytoplasm with disappearance of tigroid material and some neuronophagia.

Final diagnosis:

1. Healed endocarditis of the mitral valve and aortic cusps.
2. Acute bacterial endocarditis (*Streptococcus hemolyticus*).
3. Subarachnoid hemorrhage.
4. Meningo-encephalitis, embolic.

Case 3. J. H., colored female, aged 38. A colored female was admitted unconscious to the St. Philip Hospital on March 14, 1936. Twelve days before admission she had had a hard shaking chill while going about her usual household duties, and following this episode felt so weak that she had to go to bed. A few days after this abrupt onset, she developed a painful swelling in the left ankle and these symptoms continued unchanged until six hours before admission. At this time she had a generalized convulsion and she had remained unconscious thereafter.

Physical examination: Temperature 100.8°; pulse 90; blood pressure 118 mm. mercury systolic and 65 diastolic. An unconscious, middle-aged colored female, lying quietly in bed; respiration slow and blowing in character. The skin and mucous membranes were pale, and the face was covered with perspiration. A marked degree of nuchal rigidity was present. The chest and lungs showed no pathological change. A soft systolic murmur was noted over the cardiac apex. An indefinite mass was felt in the lower left abdominal quadrant. The left ankle was swollen, and the tissues "pitted" after digital pressure.

Laboratory data: *Urine*: heavy trace of albumin; white blood cells too many to count per high power field. *Serology*: Wassermann test negative. *Chemistry*: non-protein nitrogen 138 mg. *Spinal fluid*: 150 white cells; 90 per cent polymorphonuclear cells, 10 per cent lymphocytes.

Immediately after admission a lumbar puncture was done, and a hazy fluid under 200 mm. of pressure was obtained. The patient died about five hours after entering the hospital.

Clinical diagnosis:

1. Meningitis, type not determined.

Postmortem examination:

Autopsy diagnosis: Healed endocarditis of the mitral valve; recurrent ulcerative endocarditis of the mitral valve; firm splenic tumor (weight 280 grams); interstitial

nephritis; purulent phlegmonous salpingitis; perirectal phlegmon with suppurative phlebitis.

Brain: There was a thick creamy purulent exudate in the subarachnoid space which was most profuse over the vertex. Sections of the brain showed no further pathological lesion.

Histological examination: (Section taken to demonstrate meningitis) purulent meningitis. There were gram positive diplococci present.

Final diagnosis:

1. Healed endocarditis (rheumatic) of the mitral valve.
2. Purulent salpingitis.
3. Acute bacterial endocarditis.
4. Meningo-encephalitis; embolic.

Comment: Unfortunately, no histological examination of the brain tissue was made. From studies on other cases, an embolic encephalitis in addition to the meningitis may be surmised. This is most likely in view of the convulsive seizure which immediately preceded admission to the hospital.

Case 4. C. R., white male. A 79-year-old Italian unable to speak English was admitted to the hospital on November 22, 1935, with the diagnosis of lobar pneumonia of the left lower lobe. During the hospital stay he failed to show any prolonged duration or great elevation of temperature, and he was discharged on 12-10-35. At this time the physical signs of consolidation were still present, and the diagnosis of unresolved pneumonia was made. On 12-19-35 he was re-admitted with the history of a febrile course since discharge and progressive loss of mental alertness.

Physical examination: Temperature 102°, pulse 96, blood pressure 95 mm. mercury systolic and 65 diastolic. An irrational, stuporous white male, lying flat in bed with marked dehydration of the skin and mucous membranes. The neck was rigid and quite painful to antero-posterior motion. There was present an area of tubular breathing in the left anterior axillary line extending from the fifth to the eighth rib. The heart rate was rapid with a regular rhythm. The cardiac tones were distant, but otherwise not remarkable. The spleen was not palpated, and the extremities were negative.

Laboratory data: *Urine*: negative for albumin, sugar or pathological sediment. *Blood*: hemoglobin 90 per cent; red blood cells 3,050,000; white blood cells 14,300; 90 per cent polymorphonuclear cells; 2 per cent eosinophile cells; 8 per cent lymphocytes. *Serology*: Wassermann test negative. *Spinal fluid*: 2,450 white blood cells; 96 per cent polymorphonuclear cells. *Culture*: blood, pneumococcus; spinal fluid, pneumococcus.

Immediately after admission a lumbar puncture was done and revealed a cloudy fluid under 320 mm. of pressure. The patient died about 24 hours after admission to the hospital.

Clinical diagnosis:

1. Unresolved lobar pneumonia.
2. Pneumococcic meningitis.
3. Pneumococcic septicemia.

Postmortem examination:

Autopsy diagnosis: Subacute ulcerative endocarditis of the mitral valves; organizing pneumonia in the mid-portion and lower part of the left lower lobe; multiple myocardial scars.

Brain: On gross examination the brain was covered with a thick creamy exudate. After sectioning the vessels appeared to be very much injected, and there was a thick purulent exudate with hemorrhagic ependymitis in the ventricles. In the medulla oblongata there was a small hemorrhage measuring 3 by 3 mm.

Histological examination: Purulent meningitis with gram-positive diplococci scattered throughout the exudate. There was a fairly large area of hemorrhage and exudate cells were seen in one area in the parenchyma of the brain-stem at the level of the upper part of the fourth ventricle. Numerous petechial hemorrhages were found scattered through the brain and cord. Multiple sub-ependymal petechial hemorrhages were noted and the ependyma was covered with purulent exudative cells.

Final diagnosis:

1. Unresolved lobar pneumonia.
2. Bacterial endocarditis, acute, pneumococcic of mitral valve.
3. Ependymitis.
4. Meningo-encephalitis, embolic.

Comment: The mental status of the patient and the presence of intercerebral hemorrhages, ependymitis and the exudation of white blood cells into the brain substances substantiate the presence of an encephalitis as well as a meningitis.

Case 5. J. M., white male, aged 24. On August 8, 1936, the patient was taking a motor trip. That night he complained of sore throat and of aching all over. On the following morning he developed a diarrhea and continued to complain of aching throughout his body and feeling badly. He was seen at this time by a physician who prescribed for him but without relief of his symptoms. About 11:00 a.m. of August 10, 1936, he suddenly became irrational and violent. He remained in this condition until he was admitted to the hospital.

Physical examination: Temperature 107.4°; pulse 160; respiration 30; blood pressure 110 mm. mercury systolic and 40 diastolic. A well developed, well nourished white male, lying flat in bed completely irrational and requiring a restraining sheet. The skin was hot and dry, but otherwise negative. There were large hemorrhages present in both retinæ, and the neck was rigid. No pathological findings were present in the chest or lungs. A very harsh systolic and diastolic murmur were heard over the entire precordium. A bilateral positive Kernig reflex was present; the extremities were negative.

Laboratory data: *Blood*: red blood cells 5,385,000; hemoglobin 106 per cent; white blood cells 11,900; polymorphonuclear cells 88 per cent; lymphocytes 8 per cent; monocytes 3 per cent; myelocytes 1 per cent. *Serology*: Wassermann test negative.

Immediately after admission to the hospital a lumbar puncture was performed revealing a pink homogenous fluid under 800 mm. of pressure, containing 1,214 white blood cells; polymorphonuclear cells 94 per cent, lymphocytes 6 per cent. *Culture*: (8-11-36) spinal fluid, *Staphylococcus aureus*; blood culture, *Staphylococcus aureus*. The patient died about four hours after admission to the hospital without showing any essential changes in the original physical findings.

Clinical diagnosis:

1. Acute bacterial endocarditis of the aortic valve.
2. Meningitis.

Postmortem examination:

Autopsy diagnosis: Old healed ulcerative endocarditis of the mitral valves with superimposed verrucous endocarditis; old healed endocarditis of the aortic cusps with

superimposed verrucous endocarditis; firm splenic tumor (weight 425 grams) with multiple infarctions; embolic nephritis; multiple petechial hemorrhages in the skin and mucous membranes.

Brain: No postmortem examination.

Final diagnosis:

1. Healed endocarditis of the mitral and aortic valves.
2. Acute bacterial endocarditis (*Staphylococcus aureus*).
3. Subarachnoid hemorrhage.
4. Meningo-encephalitis, embolic.

Comment: In spite of the absence of a gross or histological examination of the brain, an assumption that this patient had an underlying embolic encephalitis in addition to the meningitis seems justified. The violent clinical onset, the hemorrhagic spinal fluid and the presence of embolic lesions of the spleen, kidney, skin and eye offer definite evidence to this effect.

Case 6. N. G., colored male, aged 27. For three weeks before admission on 5-8-37 this patient had been complaining of night sweats occurring some three to four times each week. These episodes were associated with a temperature elevation and chills lasting from one to two minutes. Since the onset of this illness his appetite had become poor, and he had had a general feeling of extreme weakness but was able to work as a truck driver up until 5-1-37. In addition to these symptoms, he also complained of palpitation of the heart and dyspnea over the past several months. On 5-3-37 he presented himself to the outpatient department and was referred from there to the hospital with a diagnosis of luetic heart disease, aortic regurgitation and possible bacterial endocarditis.

Physical examination: A well developed, and well nourished male who walked into the emergency room complaining of no acute pain and not appearing acutely ill. Temperature 101.6°, pulse 110, respiration 20, blood pressure 160 mm. mercury systolic and 70 diastolic. There were no pathologic findings on examination of the head, chest or lungs. The cardiac apex impulse was diffuse and over-active, and visualized in the fifth and sixth interspaces 12 cm. to the left of the mid sternal line. A systolic thrill was palpable over the apex. Percussion showed the left border extending 12 cm. to the left of the mid sternal line in the sixth intercostal space, and 5 cm. to the right. To and fro murmurs were heard over the aortic valve area and along the left sternal margin at the level of the fourth costal cartilage, and there was a blowing systolic murmur over the mitral area transmitted to the axilla. Examination of the peripheral vessels revealed a Corrigan pulse and pistol shot murmurs over both femoral arteries. The liver was palpated 3 cm. below the costal border, but the spleen was not palpable. The fingers showed a tendency to early clubbing.

Laboratory data: *Urine*: amber, alkaline, specific gravity 1.013, 1 plus albumin, 4-5 white blood cells and 3-4 red blood cells per high power field. *Blood*: (5-8-37) red blood cells 4,360,000; hemoglobin 89 per cent; white blood cells 28,700; 83 per cent polymorphonuclear cells, 14 per cent lymphocytes, 3 per cent monocytes. *Serology*: Kline and Wassermann tests positive. *Spinal fluid*: (5-19-37) 104 white cells, 89 per cent polymorphonuclear cells, 11 per cent lymphocytes; smear and culture were negative. *Blood culture*: (5-11, 5-18, 5-19) para-influenza bacillus.

On 5-19-37 the following note was made: "Patient has a stiff neck and complains of soreness in his muscles. He appears quite drowsy. A spinal puncture was done and a clear fluid was obtained." On 5-21-37 the spinal puncture was repeated and 5 c.c. of yellowish clear fluid removed. The pressure was 260 mm. of water. He died on 5-25-37.

Clinical diagnosis:

1. Luetic heart disease with aortic insufficiency.
2. Acute bacterial endocarditis.
3. Meningitis.

Postmortem examination:

Autopsy diagnosis: Ulcerative globular endocarditis of the aortic cusps superimposed on an old healed endocarditis; myocarditis; slight acute nonspecific aortitis; acute interstitial nephritis and early diffuse glomerulo-nephritis; anemic infarct of right kidney; scar of duodenal ulcer.

Brain: no examination.

Final diagnosis:

1. Old healed endocarditis of aortic cusps with superimposed ulcerative globular endocarditis.
2. Acute bacterial endocarditis (para-influenza bacillus).
3. Meningo-encephalitis, embolic.

Comment: The fundamental brain pathology here is probably an embolic encephalitis rather than a simple meningitis. The xanthochromic spinal fluid indicates damage to the cerebral vessels.

Case 7. D. S., colored male, aged 52, referred to the hospital because of irrational action and speech, shortness of breath and ankle edema. The present complaints had existed for three weeks prior to admission. The mental disturbance was further characterized by the obsession that inmates at the prison were trying to put poison in his food and medicine.

Physical examination: A well developed, fairly well nourished colored male, lying in bed with head and shoulders elevated. Respiration rapid and shallow. Temperature 99.2°, pulse 110, respiration 50, blood pressure 140 mm. mercury systolic and 50 diastolic. The neck veins were moderately distended and there was an area of bronchial breathing over the left apex. The cardiac rate was rapid, the rhythm regular, and the apex beat was present in the sixth intercostal space outside the mid clavicular line. A loud blowing to-and-fro murmur was present at the apex and a diastolic murmur was present over the base. The pulse was collapsing in type and Duroziez's sign was positive. On examination of the abdomen, the liver was palpable 4 cm. below the costal margin. There was definite pitting edema of both ankles and the fingers were clubbed. No abnormal neurological signs were noted.

Laboratory data: *Urine*: no pathological change. *Blood*: red blood cells 3,400,000; hemoglobin 65 per cent; white blood cells 15,500; polymorphonuclear cells 80 per cent, lymphocytes 20 per cent. *Scrology*: Wassermann test negative. *Bacteriology*: blood culture negative; gram stain from heart valve showed short chain streptococci.

Clinical diagnosis:

1. Syphilitic heart disease with aortic insufficiency.
2. Subacute bacterial endocarditis.

Postmortem examination:

Autopsy diagnosis: Healed endocarditis of aortic cusp with presence of Aschoff bodies; superimposed globular ulcerative endocarditis; septic infarction of kidney; resolving pneumonia; sickle cell anemia.

Brain: The pia-arachnoid showed edema and was focally infiltrated with many cells of the large mononuclear type. In some areas were many plasma cells, es-

pecially around the blood vessels. The ganglion cell layer of the cortex was disorganized, and in some areas most of the cells were of the glial type. There was evidence of neuronophagia and the remaining ganglion cells showed increased pigmentation. One section showed a miliary abscess containing a central clump of what appeared to be a saprophytic growth and a small clump of cocci. Scattered through the sections there were many variously sized areas of softening without septic inflammatory reaction.

Final diagnosis:

1. Healed rheumatic endocarditis of the aortic valve.
2. Acute bacterial endocarditis.
3. Meningo-encephalitis, embolic.

Case 8. P. B., white male, aged 37. The patient was in normal health until three months before admission at which time he was living in Florida and began to have hard shaking chills followed by a fever at intervals of about seven days. This continued until June 1, 1937, and since that time he has had no recurrence. His general health during this time was apparently not impaired and he had no other complaint except for frequent, drenching night sweats and pain in his left elbow, right knee and right ankle which was present from April, 1937, until the time of admission to the hospital on June 18, 1937. There was a history of chancre and of a positive Wassermann test in 1935 with nine months of intramuscular and intravenous therapy. Rheumatic fever was diagnosed at the age of 14 years.

Physical examination: The patient was a fairly well developed and poorly nourished white male, lying quietly flat in bed complaining only of pain in the left elbow. Temperature 102.6°, pulse 100, respiration 20, blood pressure 90 mm. mercury systolic and 65 diastolic. The skin had a sallow appearance. No pathological findings were noted on examining the chest and lungs. The apex beat was 9.5 cm. to the left of the mid sternal line in the sixth intercostal space; the precordium was overactive, and a systolic thrill was present at the apex. There was a loud systolic and a short diastolic murmur over the apex transmitted widely over the precordium. On abdominal examination the liver was palpable 5 cm. below the right costal margin; the spleen was definitely palpable and non-tender. There was noted a slight tendency to clubbing of the fingers and toes.

Laboratory data: *Urine*: (6-19-37) cloudy, alkaline, specific gravity 1.030, negative for albumin and sugar; sediment negative for white and red blood cells. *Blood*: (6-19-39) red blood cells 3,550,000; hemoglobin 70 per cent; white blood cells 9,950; polymorphonuclear cells 77 per cent, lymphocytes 23 per cent. *Serology*: Wassermann test negative. *Blood cultures*: (6-19, 6-22 and 6-25) positive for *Streptococcus viridans*.

Clinically the patient showed no great change during his hospital stay until July 21, 1937, when he developed a stiff neck, became drowsy and showed signs of profound shock. Lumbar puncture was performed and 12 c.c. of bloody fluid removed. Smear and culture of the spinal fluid were negative. Following the spinal puncture the patient returned to his former mental status, the headache and cervical rigidity gradually subsided, and except for marked weakness the patient returned to his former clinical condition. On August 6, 1937, he was discharged to the City Home where he died on August 9, 1937. There was no necropsy.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Subacute bacterial endocarditis.
3. Subarachnoid hemorrhage.
4. Meningo-encephalitis, embolic.

Comment: Whereas subarachnoid hemorrhage is the apparent diagnosis from the clinical and laboratory data given, the fundamental lesion is probably an embolic encephalitis. Unfortunately, he was not a patient in the hospital at the time of death, and no necropsy was performed.

Case 9. C. G., white male, aged 52. This man was in his usual state of health until January, 1937, seven months before admission to the hospital, when he began to complain of loss of weight, loss of appetite and inability to do his work. Two months before admission to the hospital he began to note the fact that his ankles would become stiff and swollen during the latter part of the day. During the latter part of May, some six weeks before admission, he developed a severe, rather sharp, intermittent and non-radiating pain in his left shoulder which was associated with a pain of similar nature over the lower left chest anteriorly. It was noted by his family physician that there was a definite friction rub over the region of this chest pain. These pains in the chest and shoulder lasted for a period of about four to six days. Otherwise his condition became progressively worse, the ankle edema failed to respond to bed rest or digitalis, and he was admitted to the hospital for further examination and treatment on July 1, 1937. No past history of rheumatic fever was obtained.

Physical examination: Temperature 100°, pulse 94, respiration 24, blood pressure 110 mm. mercury systolic and 55 diastolic. A somewhat undernourished white male with a sallow complexion, lying quietly in bed, mentally alert, rational and co-operative. Many grossly carious teeth were present. No pathological findings were noted in the chest. A systolic and diastolic murmur were heard over the aortic valve area and over the third left interspace at the sternal margin; a systolic murmur which was not transmitted was heard over the apex. No abdominal tenderness or mass was noted. The liver and spleen could not be palpated.

Laboratory data: *Urine*: (July 3, 1937), amber, acid, specific gravity 1.023, albumin and sugar negative; no white blood cells and only an occasional red cell seen. *Blood*: red blood cells 4,150,000; hemoglobin 70 per cent; white blood cells 7,500; polymorphonuclear cells 68 per cent, lymphocytes 31 per cent, monocytes 1 per cent. *Serology*: Wassermann test negative on two occasions. *Blood culture*: Eleven blood cultures were taken between the dates of June 9 and August 18, 1937, and all were reported negative.

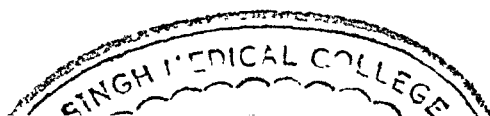
On August 11, 1937, the spleen was palpable. Five days later the patient complained suddenly of very severe headache associated with nausea, the temperature rose suddenly to 102.8° and it was noted that the neck was moderately stiff. Examination of the fundi at this time was negative. A spinal puncture was done and 20 c.c. of hazy "ground-glass" appearing fluid under 150 mm. of pressure were removed. Laboratory examination of this fluid showed: white blood cells 540, polymorphonuclear cells 81 per cent, lymphocytes 19 per cent, Wassermann test negative, smear and culture negative. Immediately following this episode the patient was extremely drowsy and lethargic, but he gradually returned to his previous mental status and by August 27, 1937, was able to be up in a chair. He was discharged to the City Home on September 1, 1937, where he died 12 days later.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the aortic valve.
3. Bacterial endocarditis.

Postmortem examination:

Anatomical diagnosis: Old healed endocarditis of the aortic valve with super-



imposed ulcerative endocarditis; cardiac hypertrophy and dilatation; healed infarct of the spleen; chronic passive congestion of the liver.

Brain: No postmortem examination.

Final diagnosis:

1. Healed endocarditis of aortic cusps (rheumatic).
2. Subacute bacterial endocarditis.
3. Meningo-encephalitis, embolic.

Case 10. H. W., colored male, aged 15. One week before the present admission on June 13, 1938, this young boy began to complain of a severe generalized headache and a constant dull pain over the back of his neck. Two days before admission he suddenly lost the use of his left arm and leg and, because this condition failed to improve, he was brought to the hospital. About six months prior to this occurrence he had been treated for acute rheumatic heart disease. The interval history was not eventful.

Physical examination: Temperature 103.2°; pulse 96; respiration 24; blood pressure 140 mm. mercury systolic and 10 diastolic. The general appearance was that of a poorly developed, emaciated colored male lying flat in bed complaining of pain in the back of the neck. There was a flaccid paralysis of the left arm and leg. The left side of the face was smooth and expressionless. Numerous petechial hemorrhages were present in both conjunctivae. There was no stiffness or tenderness of the neck, and the chest and lungs were normal. The cardiac apex was palpable in the fourth intercostal space in the mid axillary line with a palpable thrill in the region of the left nipple. A loud to-and-fro murmur was present over the entire precordium but loudest over the pulmonic valve area. A presystolic murmur was audible in the region of the left nipple. The spleen could not be palpated. In addition to the flaccid paralysis of the left arm and leg, a small petechial hemorrhage was present at the tip of the second finger of the left hand. The fingers were not clubbed.

Laboratory data: *Urine*: many red blood cells were noted on June 18, 1938. *Blood*: hemoglobin 52 per cent; white blood cells 17,100. *Chemistry*: formol-gel negative. *Spinal fluid*: white blood cells 45; polymorphonuclear cells 7, lymphocytes 38, culture negative. *Blood culture*: positive for *Streptococcus viridans*.

A lumbar puncture was done on June 16, 1938, and showed a clear fluid under normal pressure. There were present 45 white blood cells of which 38 were lymphocytes and 7 polymorphonuclear cells. On June 21, 1938, a beginning clubbing of the fingers was noted. Because no specific medication or treatment could be recommended he was discharged on July 17, 1938. On August 17, 1938, he returned to the hospital because of gangrene of the left foot and died August 18, 1938, the day following amputation.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the mitral valve and aortic cusps.
3. Subacute bacterial endocarditis.
4. Left hemiplegia due to cerebral embolus.

Postmortem examination:

Anatomical diagnosis: Globular ulcerative bacterial endocarditis of the mitral valve and aortic cusps; aortic and mitral insufficiency; septic thrombosis of a branch of the mesenteric artery and infarction of the small intestine (ileum); multiple old and recent bland anemic infarctions of the kidney and spleen; thrombosis of a branch of the right coronary artery.

Brain: No postmortem examination.

Final diagnosis:

1. Rheumatic heart disease with chronic rheumatic endocarditis of the mitral valve and aortic cusps.
2. Subacute bacterial endocarditis.
3. Left hemiplegia due to cerebral embolus.
4. Meningo-encephalitis, embolic.

Comment: With the presence of an increase of white blood cells in the spinal fluid, it is probable that there were widespread embolic lesions of the brain and that the patient had a true embolic encephalitis as well as an arterial occlusion.

Case 11. V. S., white female, aged 18. Seven days before admission this patient developed a right sided headache associated with nausea, vomiting and mental confusion. These complaints had been preceded by an upper respiratory infection of about 10 days' duration. During an examination of the sinuses, ears and mastoids a stiff neck was noted and a tentative diagnosis of meningitis was made. A lumbar puncture revealed bloody fluid under pressure, and the patient was referred to the hospital with the diagnosis of a right frontal lobe tumor.

Physical examination: Temperature 102.8°; pulse 96; respiration 22; blood pressure 155 mm. mercury systolic and 40 diastolic. The general appearance was that of a fairly well developed and nourished individual in a confused semi-stuporous mental state. Grossly there was evidence of a flaccid paralysis of the left arm and leg and a left facial weakness of the central type. Nuchal rigidity was present. The chest and lungs were normal. The cardiac apex was palpated in the fifth intercostal space 11 cm. from the mid sternal line, and a loud to-and-fro murmur was audible over the entire precordium. The pulse was collapsing in type. The spleen was palpable. No clubbing of the fingers was noted. In addition to the left hemiplegia, the Kernig and Brudzinski reflexes were bilaterally positive, and the right abdominals were hyperactive.

A lumbar puncture done shortly after admission revealed a xanthochromic fluid under 265 mm. of pressure.

Laboratory data: *Urine*: 1-4 red blood cells per high power field. *Blood*: red blood cells 3,770,000; hemoglobin 64 per cent; white blood cells 20,650; polymorphonuclear cells, 86 per cent, lymphocytes 13 per cent, monocytes 1 per cent. *Spinal fluid*: white blood cells 77; polymorphonuclear cells 44; lymphocytes 43; culture negative. *Blood culture*: *Streptococcus viridans*.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral and aortic valves.
3. Subacute bacterial endocarditis.
4. Left hemiplegia due to cerebral embolus.
5. Meningo-encephalitis, embolic.

Postmortem examination: none made.

Comment: The mental symptoms, nuchal rigidity and increase in the cellular elements of the spinal fluid point to widespread embolic lesions (embolic encephalitis) of the brain rather than simple arterial occlusion.

Case 12. E. S., white female, aged 53. This patient was brought to the hospital because of her inability to talk or to use her right arm and leg. For the past six to eight years she had not felt entirely well and for the past three to four years

this feeling had been characterized by shortness of breath on exertion, swelling of the ankles and easy fatigability. In February, 1935, two months before admission to the hospital, there were two acute episodes characterized by cough, dyspnea and cyanosis which were diagnosed as heart attacks. On the morning of admission, the patient was found in bed unable to talk or to move her right arm and leg.

Physical examination: Temperature 100°, pulse 110, blood pressure 134 mm. mercury systolic and 70 diastolic. A white female lying flat in bed, aphonic and unable to move her right arm or leg. The skin was pale with a suggestive café-au-lait tint and multiple petechiae were present. Moist râles were heard in both lung bases. A harsh systolic murmur replacing the first sound was present at the cardiac apex and followed by a loud snapping second sound. A systolic thrill was present over the apex. The spleen was not palpable. No clubbing of the fingers or toes was noted.

Laboratory data: *Urine*: albumin 2 plus; 10-15 white blood cells and rare red blood cell per high power field. *Blood*: hemoglobin 34 per cent; white blood cells 6,000. *Blood culture*: positive for *Streptococcus viridans*.

Diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with right hemiplegia and aphonia.

Case 13. H. G., white female, aged 36. The patient had been in good health until four weeks before admission on September 12, 1934. Since this time she had complained of a dry cough, shortness of breath, soreness in her anterior chest, headache and a feeling of numbness in both hands. For several weeks she had been having frequent chills or chilly sensations. Three years ago she had had pneumonia which left her with a "weakened heart." Thereafter chills and coughing attacks had occurred frequently.

Physical examination: Temperature 104°, pulse 100, blood pressure 105 mm. mercury systolic and 65 diastolic. A well developed white female lying flat in bed but restless on account of a persistent hacking cough. The skin had a sallow appearance. A moderate degree of distention of the neck veins was present. Medium moist râles were heard in both lung bases. There was present a systolic murmur over the apex transmitted over the entire precordium and into the axilla. This murmur was harsh and rumbling in character and preceded by a presystolic murmur. The pulmonic second sound was accentuated. The liver was palpated 3 cm. below the costal margin. The fingers showed very early clubbing. The neurological examination and reflexes were negative.

Laboratory data: *Urine*: rare red blood cell. *Blood*: hemoglobin 84 per cent; red blood cells 4,600,000; white blood cells 8,600; polymorphonuclear cells 84 per cent, lymphocytes 15 per cent; monocytes 1 per cent. *Serology*: Wassermann negative. *Blood culture*: four cultures were reported negative.

On September 17, 1934, the patient suddenly had a severe chill and immediately thereafter developed a complete left hemiplegia.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with left hemiplegia.

Case 14. O. S., colored female, aged 18. Four weeks before entering the hospital on September 13, 1935, this patient developed a febrile illness which was charac-

terized by extreme weakness and headache. The temperature elevation was constant in nature, but there had been no chills. Two days before admission she developed severe, intractable pain in the upper portion of both thighs.

Physical examination: Temperature 102°, pulse 126, blood pressure 105 mm. mercury systolic and 55 diastolic. A well developed colored female, lying flat in bed complaining severely of pain in both thighs. There was marked pallor of the conjunctivae. The breath sounds in the left base were bronchovesicular in character. Both cardiac tones were loud and snapping in character, particularly the first. There was present a soft apical systolic murmur. The spleen could be palpated. There was an early clubbing of the fingers.

Laboratory data: *Urine*: trace of albumin; 15-20 red cells per high power field. *Blood*: red blood cells 2,710,000; hemoglobin 40 per cent; white blood cells 17,100. *Serology*: Wassermann test negative. *Blood culture*: *Streptococcus viridans*.

On December 1, 1935, she suddenly became unconscious, and on examination was found to have a complete right hemiplegia and multiple emboli to both fundi.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with right hemiplegia.

Case 15. M. B., colored female, aged 19. For two years prior to the present illness, this patient had been troubled with vague, transitory pains in both feet, ankles and hips which at times were associated with swelling of the feet. For two months before admission on April 2, 1936, she had noticed shortness of breath which at first occurred only after exertion, but later became so severe that she required two pillows to sleep comfortably.

Physical examination: Temperature 98°, pulse 105, respiration 36, blood pressure 120 mm. mercury systolic and 90 diastolic. A poorly nourished, emaciated colored female lying propped up in bed. The conjunctival mucous membrane was pale. On examination of the heart the apex beat was noted in the fifth intercostal space 11 cm. from the midsternal line, and it was forceful in character. A loud blowing systolic and diastolic murmur were heard over the mitral valve area. The systolic phase was noted over the entire precordium. The liver was palpable 1.5 cm. below the costal margin, and the spleen was firm and palpable. Marked clubbing of the fingers and toes was present.

Laboratory data: *Urine*: negative for red blood cells. *Blood*: red blood cells 3,510,000; hemoglobin 60 per cent; white blood cells 10,700; polymorphonuclear cells 76 per cent; lymphocytes 23 per cent; monocytes 1 per cent. *Serology*: Wassermann test strongly positive. *Blood culture*: *Streptococcus viridans*.

On April 21, 1936, the patient suddenly developed a complete left hemiplegia of the central type. She was discharged from the hospital three days later, at the request of her husband.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral and aortic valves.
3. Congestive heart failure.
4. Subacute bacterial endocarditis.
5. Cerebral embolus with left hemiplegia.

Case 16. R. M., white female, aged 22. The patient had been in good health until March 9, 1933, when she developed a severe pain in the left lower quadrant.

Seen by a physician at this time she was told that she was seven months' pregnant and had "pus tubes." On April 8, she was delivered of a stillborn infant and immediately thereafter began to show marked increase in temperature associated with chills and sweats. This state failed to improve with treatment and she was referred to the hospital on May 13, 1933.

Physical examination: Temperature 99°, pulse 100, respiration 20, blood pressure 110 mm. mercury systolic and 70 diastolic. Examination revealed a white female, well developed but poorly nourished and showing a definite pallor of the skin and mucous membranes. Medium moist râles were present over both apices. The cardiac impulse was palpated in the sixth intercostal space 13 cm. from the mid sternal line, and there was a systolic thrill over this region. The first sound at the apex was short and followed by a blowing systolic murmur. Over the pulmonic area the first sound was accentuated and reduplicated. On one occasion a gallop rhythm was noted. Definite clubbing of the fingers was noted, but the spleen could not be palpated and no petechiae were present. A large tender mass was felt in the left adnexia.

Laboratory data: *Urine*: trace of albumin; rare red blood cell. *Blood*: red blood cells 3,080,000; hemoglobin 55 per cent; white blood cells 18,300; polymorphonuclear cells 80 per cent, lymphocytes 18 per cent, eosinophiles 1 per cent, monocytes 1 per cent. *Serology*: Wassermann test negative. *Blood culture*: *Streptococcus viridans*.

On May 22, 1933, the patient suddenly developed left facial paralysis of the central type and definite weakness of the left arm and leg with positive clonus, Babinski and hyperactive deep reflexes on this side. A spinal fluid revealed a clear fluid under 220 mm. of pressure; white blood cells 48, polymorphonuclear cells 32, lymphocytes 16, Wassermann test negative. The culture on this fluid was not reported. The patient died July 6, 1933.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Left hemiplegia due to a cerebral embolus.

Postmortem examination:

Anatomical diagnosis: Subacute vegetative endocarditis of the mitral valve; firm splenic tumor (weight 425 grams); anemic infarcts of the spleen and kidneys; embolic phenomena of skin; pulmonary tuberculosis.

Brain: No postmortem examination.

Final diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Pulmonary tuberculosis.
5. Cerebral embolus with left hemiplegia.

Comment: The increase in the cellular elements of the spinal fluid indicates a more widespread embolic damage to the brain than simple arterial occlusion. It is our impression that histological study of the brain would have shown an embolic encephalitis.

Case 17. M. W., white female, aged 42. This patient was admitted to the hospital on July 2, 1934, with the history of having been in good health until July, 1933, at which time she had had 17 teeth extracted because of apical abscesses. Four days

later she fainted while going up a flight of steps, fell and fractured her skull in the frontal region. She was operated on for this three days later and has since this time suffered acutely with severe pain in this region. For two weeks prior to admission she had had a constant afternoon temperature, reaching a peak of 103°. She entered the hospital on the neurosurgical service.

Physical examination: Temperature 99.8°, pulse 85, respiration 20. No evidence of an operative type of lesion of the brain or skull was found after neurological examination, and the following observations were noted by the medical consultant. The skin and mucous membranes showed definite pallor with slight pigmentation of the skin typical of the café-au-lait tint. The cardiac apex was palpated in the fifth interspace 8.5 cm. from the midsternal line with a diastolic thrill present in this region. There was present here a diastolic murmur, and the first sound was loud and snapping. Over the pulmonic area the second sound was accentuated. The spleen was palpable 4 cm. below the left costal margin. Definite clubbing of both the fingers and toes was present.

Laboratory data: *Urine*: slight trace of albumin. *Blood*: hemoglobin 72 per cent; white blood cells 9,500; polymorphonuclear cells 81 per cent, lymphocytes 18 per cent, eosinophiles 1 per cent. *Blood culture*: *Streptococcus viridans*.

She was discharged from the hospital on July 5, 1934, and re-admitted on August 12, 1934, with complete left hemiplegia. She died on August 13, 1934.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve and aortic cusps.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with left hemiplegia.

Postmortem examination: Not made.

SUMMARY

The fundamental pathologic change in the central nervous system in cases of bacterial endocarditis is a diffuse embolic meningo-encephalitis, and from this the various clinical manifestations arise. The types of lesions are pleomorphic and no local area of the brain appears to be predisposed to injury. As a consequence, the clinical neurologic manifestations are not absolutely predictable. There does occur, however, a broad pattern to which these signs adhere, and it is to this that we wish to direct special attention.

Meningitis: Of all the clinical manifestations of central nervous system damage, meningitis appears the most frequently. In varying degrees of severity it was noted in 11 of the 17 cases, and occurred most often and was most severe in cases of acute bacterial endocarditis. Nuchal rigidity and spinal fluid changes were common features of all. Opisthotonos, positive Brudzinski and positive Kernig's signs were sometimes present. Often the meningitis was present in conjunction with other neurological changes such as subarachnoid hemorrhage, hemiplegia as a result of gross arterial occlusion, hemorrhagic ependymitis and intra-ventricular hemorrhage. For the most part the cellular response showed a high percentage of polymorphonuclear cells, but in a definite number of instances lymphocytes and mono-

cytes predominated. In the cases of acute bacterial endocarditis, the organism responsible for the valvular lesion and present in the blood stream was recovered in four of six cases. In the cases of subacute bacterial endocarditis, the causative organism was not recovered in a single one of the five cases in which the spinal fluid was studied. A review of the literature confirmed this observation, and we were able to find reference to only one case⁹ in which the *Streptococcus viridans* was recovered from the spinal fluid. This fact seems highly significant, and has led us to make very close and thorough investigation for the presence of a viridans endocarditis in all patients with a so-called "sterile meningitis"⁵ which is not otherwise adequately explained.

Hemiplegia: Hemiplegia of a central type as a result of large cerebral emboli occurred in eight cases and was the next most frequent neurologic finding. This type of lesion was associated only with the subacute bacterial endocarditis cases. In three instances there was present also a meningitis, but in the remainder of the cases there was no clinical evidence of brain damage beyond the area supplied by the occluded artery. Aphonia accompanied the hemiplegia in only one instance.

In addition to these two outstanding clinical manifestations of central nervous system damage, the following changes were noted.

Subarachnoid hemorrhage: Gross blood in the spinal fluid was noted in three cases. This was present only in cases of acute bacterial endocarditis and was always associated with a meningitis.

Psychosis: A fully developed psychosis with delusions of persecutions was noted once. Clinically this was accompanied by a meningitis, and pathologically it was associated with a diffuse meningo-encephalitis.

Aphonia: This was present in one case and was associated with a hemiplegia as a result of a cerebral embolus.

Two patients were unconscious when admitted to the hospital, and two were irrational.

Headache, dizziness, auditory hallucinations, stupor, drowsiness and mental confusion occurred frequently in the symptomatology of the group.

Table 1 tabulates the neurologic signs and symptoms, and also lists the general physical signs occurring in the cases of bacterial endocarditis studied.

Spinal fluid: Examinations were made on the spinal fluid in 11 of the cases and the results are tabulated in table 2. For the most part these are self-explanatory. Consideration is given only to the pressure readings, the cytology and the bacteriological aspects as the other studies contributed no essential findings. In only one instance was the pressure elevated to an abnormal degree (Case 5). In this case the patient was violent, irrational and the victim of an overwhelming staphylococcic infection with a severe meningitis and subarachnoid hemorrhage. In three other cases pressure readings above 200 mm. were noted. The cellular response was varied in both degree and in character, and the cell counts ranged from 45 to 2,450 white blood cells per cubic mm. In character the cells for the most part showed a high

TABLE I

Case	Neurological		General Physical Signs	Neurological Diagnosis	Blood Culture
	Symptoms	Signs			
1 Acute bacterial endocarditis	None	Nuchal rigidity, spinal fluid *	Signs of valvular heart disease: absent Palpable spleen: not palpable (200 gm. post mortem) Clubbed fingers: present Skin and mucous membranes: negative	1. Meningo- encephalitis (post mortem)	Pneumococcus
2 Acute bacterial endocarditis	Headache, dizziness, auditory hallucinations	Lethargy, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: petechiae	1. Meningo- encephalitis 2. Subarachnoid hemorrhage 3. Intracerebral hemorrhage	Hemolytic streptococcus
3 Acute bacterial endocarditis	Convulsions	Loss of consciousness, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: absent Palpable spleen: not palpable (280 gm. post mortem) Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo- encephalitis (post mortem)	Pneumococcus ?
4 Acute bacterial endocarditis	Stupor	Irrational, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: absent Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo- encephalitis 2. Hemorrhagic ependymitis	Pneumococcus
5 Acute bacterial endocarditis	None	Irrational, violent, retinal hemorrhage, positive Kernig's sign, nuchal rigid- ity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo- encephalitis 2. Subarachnoid hemorrhage (post mortem, no brain)	<i>Staphylococcus aureus</i>
6 Acute bacterial endocarditis	Headache, drowsiness	Drowsy, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: negative	1. Meningo- encephalitis (post mortem, no brain)	Parainfluenza bacillus

* See table 2.

TABLE I—Continued

TABLE 1—Continued					
Case	Neurological		General Physical Signs	Neurological Diagnosis	Blood Culture
	Symptoms	Signs			
7 Subacute bacterial endocarditis	None	Delusions of persecution	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: negative	1. Meningo-encephalitis (post mortem)	Short chain gram positive streptococcus
8 Subacute bacterial endocarditis	Headache	Nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: café-au-lait	1. Meningo-encephalitis 2. Subarachnoid hemorrhage	<i>Streptococcus viridans</i>
9 Subacute bacterial endocarditis	Headache	Stupor, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: pallor Skin and mucous membranes: present	1. Meningo-encephalitis (post mortem, no brain)	Negative repeated
10 Subacute bacterial endocarditis	Headache, loss of use of left arm and leg	Hemiplegia, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo-encephalitis 2. Cerebral embolus (post mortem, no brain)	<i>Streptococcus viridans</i>
11 Subacute bacterial endocarditis	Headache, confused	Stuporous, hemiplegia, left, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: negative Skin and mucous membranes: present	1. Meningo-encephalitis 2. Cerebral embolus (left)	<i>Streptococcus viridans</i>
12 Subacute bacterial endocarditis	None	Aphonia, hemiplegia, right	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: café-au-lait, petechiae	1. Cerebral embolus	<i>Streptococcus viridans</i>

TABLE I—Continued

Case	Neurological		General Physical Signs	Neurological Diagnosis	Blood Culture
	Symptoms	Signs			
13 Subacute bacterial endocarditis	Headache	Hemiplegia, left	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: café-au-lait	1. Cerebral embolus	Negative
14 Subacute bacterial endocarditis	Headache	Hemiplegia, right	Signs of valvular heart disease: absent Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: pallor	1. Cerebral embolus	<i>Streptococcus viridans</i>
15 Subacute bacterial endocarditis	None	Hemiplegia, left	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: pallor	1. Cerebral embolus	<i>Streptococcus viridans</i>
16 Subacute bacterial endocarditis	None	Hemiplegia, left, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: pallor	1. Cerebral embolus	<i>Streptococcus viridans</i>
17 Subacute bacterial endocarditis	Frontal headache	Hemiplegia, left	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: café-au-lait	1. Cerebral embolus	<i>Streptococcus viridans</i>

TABLE II

Case No.	Type	W.B.C.	P.M.N.	Lymphs	R.B.C.	Pressure	Culture
1.	Acute bacterial endocarditis	1200	96%	4%	0	175	Negative
2.	Acute bacterial endocarditis	403	88%	12%	1650		<i>Streptococcus hemolyticus</i>
3.	Acute bacterial endocarditis	150	90%	10%			Gram positive diplococci (smear)
4.	Acute bacterial endocarditis	2450	96%	4%	Gross	800	<i>Pneumococcus</i>
5.	Acute bacterial endocarditis	1214	94%	6%	Gross	260	<i>Staphylococcus aureus</i>
6.	Acute bacterial endocarditis	276	73%	27%			Negative
8.	Subacute bacterial endocarditis					150	Negative
9.	Subacute bacterial endocarditis	540	81%	19%			Negative
10.	Subacute bacterial endocarditis	45	7	38			Negative
11.	Subacute bacterial endocarditis	77	33	44		265	Negative
16.	Subacute bacterial endocarditis	48	32	16		220	Negative

percentage of polymorphonuclear leukocytes, but in some instances the lymphocytes showed a marked predominance. This was in keeping with pathologic findings in which areas of monocytic meningitis were often found associated with areas of polymorphonuclear cell infiltration. The bacteriological studies have already been discussed.

CONCLUSIONS

1. The fundamental brain pathology in bacterial endocarditis is a diffuse embolic meningo-encephalitis.

2. Embolic brain lesions are an important part of the pathologic anatomy of bacterial endocarditis, and frequently produce the outstanding clinical features of the syndrome.

3. The presence of a "sterile meningitis" in any case of an obscure febrile illness should always suggest the possibility of a viridans endocarditis.

4. The triad of clubbed fingers (Hippocratic), splenomegaly, and meningo-encephalitis is presumptive evidence of acute bacterial endocarditis in spite of the absence of signs of cardiac lesions.

BIBLIOGRAPHY

1. OSLER, WILLIAM: Malignant endocarditis, Brit. Med. Jr., 1885, i, 467; Lancet, 1885, i, 415.
2. KIMMELSTIEL, PAUL: Ueber Viridans-Encephalitis bei Endocarditis Lenta, Beitr. z. path. Anat. u. z. allg. Path., 1927, lxxix, 39.
3. DIAMOND, J. B.: Brain changes in malignant endocarditis, Arch. Neurol. and Psychiat., 1932, xxvii, 1175.
4. DEJONG, RUSSEL N.: Central nervous system complications in subacute bacterial endocarditis, Jr. Nerv. and Ment. Dis., 1937, lxxxv, 397.
5. LIBMAN, E.: The clinical features of subacute streptococcus endocarditis in the bacterial stage, Med. Clin. N. Am., 1918, ii, 117.
6. WINKELMANN, N. W., and ECKEL, JOHN L.: The brain in bacterial endocarditis, Arch. Neurol. and Psychiat., 1930, xxiii, 1161.
7. LEREBoullet, P., and MOUZON, J.: Forme méningitique de l'endocardite maligne à évolution lente, Bull. et mém. Soc. méd. d. hôp. de Paris, 1920, xlv, 894.
8. SMITH, F. J., and BRUMFIEL, D. M.: Meningitis complicating subacute bacterial endocarditis, Am. Heart Jr., 1927, ii, 446.
9. TICE, FREDERICK: Acute endocarditis with complicating meningitis, Med. Clin. Chicago, 1916, i, 625.
10. ULLOM, J. T.: Subacute endocarditis simulating meningitis, Arch. Neurol. and Psychiat., 1929, xxi, 418.
11. CABOT, R. C.: Acute and subacute endocarditis; facts on the heart, 1926, W. B. Saunders Co., Philadelphia, p. 617.
12. DENMAN, H. C.: Subacute endocarditis; six cases with autopsy findings, Internat. Clin., 1932, ii, 131.
13. BLUMER, GEORGE: Subacute bacterial endocarditis, Medicine, 1923, ii, 105.
14. FIESSINGER and JANET: La forme 'raccourcie' de l'endocardite maligne du type Jaccoud-Osler, Bull. et mém. Soc. méd. d. hôp. de Paris, 1920, iv, 1443.
15. NADLER, W. H., and HERNDON, R. F.: Recurrent *Streptococcus viridans* endocarditis with unusual meningeal complication, Illinois Med. Jr., 1917, xxxi, 339.

16. POL: Embolisches infektiöses Aneurysma der A. cerebr. post. dextra. bei 'Endocarditis lenta,' München. med. Wchnschr., 1922, lxix, 417.
17. RABINOWITZ, M. A., MARCUS, I. H., and WEINSTEIN, JOSEPH: Subacute bacterial endocarditis with large brain abscess, Jr. Am. Med. Assoc., 1932, xcvi, 806.
18. RANDOLPH, B. M.: Acute vegetative endocarditis accompanied by cerebral embolism, Va. Med. Month., 1931, lviii, 98.
19. SCHOTTMÜLLER, H.: Endocarditis lenta, Münch. med. Wchnschr., 1910, lvii, 617.
20. ISTAMONOWA, T.: Histological findings in endocarditis lenta, Virchow's Arch. f. path. Anat., 1928, cclxviii, 224.
21. HEINEMANN, H. N.: Cerebro-spinal meningitis, acute endocarditis and pericarditis, Med. Rec., 1881, xx, 746.
22. CLAUDE, HENRI: Forme nerveuse de l'endocardite à évolution lente, Bull. Acad. de méd., 1918, lxxix, 211.
23. WALDMAN, D. P., and KAHN, M. H.: Subacute infective endocarditis with mycotic aneurysm and meningeal symptoms, N. Y. State Med. Jr., 1925, xxvi, 667.
24. VAPUEX, LAIDLAW: Acute endocarditis, Diseases of the heart, 1924, W. B. Saunders Co., Philadelphia, p. 251.
25. UNTERSTEINER, R.: Pneumococcus meningo-encephalitis with particular regard to exudation of fibrin in the central nervous system, Ztschr. f. d. ges. Neurol. u. Psychiat., 1926, cii, 64.
26. NATHAN, HELMUTH: Ueber Viridans Encephalitis, Ztschr. f. d. ges. Neurol. u. Psychiat., 1930, cxxvi, 536.
27. WOHLWILL, FRIEDRICH: Sobre a encefalite embólica na endocardite lenta e especialmente sobre as lesões do corno de Ammon nesta afecção, Lisboa Med., 1938, xv, 54.

TUBERCULOSIS AMONG STUDENTS AND GRADUATES OF MEDICINE*

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THE problem of tuberculosis among students and graduates of medicine has been present since the earliest days of medical practice. Valsalva, the anatomist (1666-1723), avoided postmortem examinations when the cause of death was consumption. Morgagni, his pupil (1682-1771), continued this practice avoiding them in order to protect his students as well as for personal reasons. Isocrates (436-338 B.C.), Aristotle (384-322 B.C.), and Galen (131-201 A.D.) appreciated the contagiousness of tuberculosis. Laennec, himself, infected his left index finger while performing a post-mortem examination about 1800 and died of consumption in 1826.

In 1818 Armstrong said: "When young men enter upon the study of medicine, they occasionally break up their general strength by the intensity of their applications in the dissecting rooms, in the tainted air of a hospital, or in their own apartments, and may actually become consumptive from this cause." Long before and ever since Armstrong made this statement, similar factors have been cited to account for tuberculosis among medical students and physicians. We now assign the cause of diphtheria to the diphtheria bacillus and have relegated to the discard all the opinions of the past. We have equally good reason to assign the cause of tuberculosis to the tubercle bacillus. Of the secondary factors which are so freely discussed, we are not certain of one.

Because of the rapid decline of tuberculosis in the general population, the disease among physicians as well as other members of hospital personnel has become more conspicuous. Moreover, modern aids in diagnosis have enabled physicians to diagnose the disease in its clinical forms months and even years before physicians of two or three decades ago could possibly have recognized it. Even the first infection type of tuberculosis may often be detected as to location in the living if adequate examination is made; whereas, only a short time ago this type of tuberculosis was located only at post-mortem examination.

In a few medical schools, observations have been made on the incidence of tuberculin reactors among the students. For example, in 1931 Hetherington et al. tested 452 medical students at the University of Pennsylvania and compared the findings with those of high school boys in Philadelphia.

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In the high school group they found 77.8 per cent reacted to the tuberculin test but in the medical school group the incidence of reactors was 93.6 per cent. In the senior medical class, however, 98.2 per cent of the students reacted to tuberculin. Herman et al. found that 79 per cent of the first year medical students at Johns Hopkins University reacted to tuberculin as compared to approximately 100 per cent of students in the third and fourth years. These and other reports have indicated that the infection attack rate among students of medicine is high.

Demonstrable lesions in medical students and physicians have also been investigated in recent years. Soper and Amberson state that at the Yale school of medicine, tuberculosis has not been a major problem. Among 427 students who entered the school from 1930 through September 1937, six had parenchymal lung lesions on entrance; three developed minimal apical lesions; one subapical disease; and two fell ill during their course. Thus, they conclude that six of the twelve students who had clinical tuberculosis possibly contracted infection or superinfection during the medical course. The situation existing in other schools of medicine as obtained through correspondence with Student Health Services, physicians, etc., is also reported. In summarizing this work on medical students, Soper and Amberson state: "They are, as a rule, less rapidly and less certainly infected than pupil nurses, but they still acquire infection to an excessive degree. The morbidity among them appears to vary. It seems alarmingly high in a few instances, but not in the majority of schools whose figures are known. Many of the leading schools have already instituted programs of prevention and case finding. Where a definite program is lacking there is an increasing consciousness of the problem and effort to cope with it. The mortality seems not unduly high, probably because the cases developing are apt to be diagnosed and treated early."

Chadwick's observations led him to state that "There is a much higher incidence of tuberculosis among nurses, medical students and doctors during their first years of practice than in the general population."

Vaucher et al. of the University of Strasbourg began making examinations of students in 1929. They observed several students who became tuberculin reactors soon after ward work was begun and described the ensuing demonstrable lesions, noting the absence of symptoms in the majority of cases. In discussing this paper, Rist of Paris pointed out that his experience with many students confirmed that of Vaucher and that at the University of Minnesota.

Scheel of Oslo observed medical students between 1926 and 1936. The annual morbidity rate was 4.8 per cent among those who entered school as non-reactors to tuberculin, and 1.1 per cent among those who entered as reactors. The morbidity rate among the non-reactors compared with the reactors was 4 to 1. He found that the maximum tuberculosis morbidity and mortality are observed during the first three years after primary infection, chiefly

during the first year. The morbidity from pleurisy is 9 per cent during the first year.

Jacob in discussing the first infection type of tuberculosis points out the difficulty in differentiating it from the reinfection type in the absence of tuberculin tests as follows: "In fact, neither by the seat of the lesion, nor by its radiological appearance does a primary tuberculosis infection essentially differ from reinfection. The author therefore believes that so long as one does not investigate and register regularly and periodically the results of the tuberculin test in the school, the army, the factory, the shops and the colleges, the notion of primary infection however interesting, will not become a clinical fact which must be taken into account when establishing a prognosis or deciding upon a course of treatment. Clinical investigation does not enable one to differentiate with certainty or even with much probability a primary tuberculosis infection from a re-infection."

Hetherington et al. found that evidence of disease at the apices of the lungs increased definitely from year to year among medical students. Among the freshmen in only 4.1 per cent was such evidence revealed. This percentage increased to 11.6 in the junior year and 20.5 in the senior year.

Pepper in discussing the incidence of tuberculosis among medical students at the University of Pennsylvania as reported by Hetherington et al. states: "Our students handle specimens removed at autopsies made on tuberculous patients. Very much of our clinical teaching is done at the Philadelphia General Hospital which cares for a large number of tuberculous patients. But our medical students do not seem to be more liable to other ailments than the rest of the university students." In commenting on Dr. Pepper's presentation Harvey says: ". . . that it is time for us, as an Association (Association of American Medical Colleges) and for our schools individually, to pay more attention to the health of students. Clearly, it is time to do so, for neglect of the student's health is lamentable in the college and it becomes almost criminal in a medical school."

Lees says: "The problem of tuberculosis among medical students at the University of Pennsylvania has been given special study and consideration during the past three years by a faculty committee appointed by Dean William Pepper. The prevalence of the disease among our students of medicine has been significantly greater than that encountered in students of other schools on the campus. Moreover, the development of new lesions has been observed chiefly in members of the third and fourth year classes. The distribution of cases in the clinical years of training as contrasted with the non-clinical years, approximately eight to one, has followed much the same pattern during the past five years. However, the incidence of tuberculosis of the reinfection type among medical students has fallen from 5.8 per cent in the school year 1935-1936 to 3.9 per cent at the present time. During this period various procedures have been planned with the idea of reducing to a minimum the student's opportunity for infection with tubercle bacilli. The use of tuberculous patients for second year classes in physical diagnosis has

been discontinued. The department of pathology has carefully revised the technic employed in the autopsy room and gives systematic instruction to students regarding the hazards of various types of infections from laboratory sources. In the tuberculosis clinics conducted by the department of medicine, a very limited number of positive sputum cases are used for demonstration purposes and the conduct of patient and student is carefully supervised. In view of the fact that approximately 90 per cent of our medical students are allergic to tuberculo-protein at the beginning of the third year and since the development of pulmonary tuberculosis reaches its peak in the particular age zone represented by a majority of this group, it would seem mandatory that every possible protection should be given the student against possible infection with tubercle bacilli."

In the report from the Central State Hospital at Indianapolis, Indiana, for 1932 the following statements are made: "Since 1896 all the autopsies were performed in the large amphitheater, which is also used for clinical instruction of medical students, nurses, and social workers. During the performance of every autopsy on patients who died of an infectious disease such as miliary or pulmonary tuberculosis, streptococcic septicemia, typhoid fever, there is a certain spreading of infectious organisms. It is practically impossible to disinfect safely the autopsy table and its immediate surroundings after every autopsy. In the interest of the students who receive clinical instruction in the amphitheater we removed the autopsy table to other quarters, since in our opinion the postmortem table and its surroundings constitute at times a distinct health hazard." The pathologist and director of research of this institution, Dr. Walter L. Bruetsch, had been convinced that at least some of the tuberculosis among students was due to infection from the postmortem room.

Bates found that 7.1 per cent (239) of 3,349 patients discharged from the Trudeau Sanatorium between 1916 and 1931, were medical students and physicians. Of these, only a slightly greater proportion had their disease detected earlier than those engaged in other activities of life. This is not surprising when one considers that between 1916 and 1931 routine tuberculin tests were not administered to adults and the roentgen-ray film was employed mostly as a confirmatory measure, that is, after symptoms were present or physical signs were elicited. Significant symptoms usually mean moderate or far advanced disease. With routine and periodic tuberculin testing and roentgen-ray film examinations now in practice among medical students, one rarely sees a diagnosis first made after the disease is advanced.

There are reports in the literature which show a low incidence of clinical tuberculosis among physicians. For example, Laird records 57 physicians who have been employed at the Nopeming Sanatorium, six of whom were tuberculous before entering the service; three who began the service as non-reactors later reacted to tuberculin; one other physician after leaving the sanatorium had a pulmonary hemorrhage. Pollock and Forsee found only 1.7 per cent of 227 physicians developed clinical tuberculosis. Space does

not permit us to present all of the papers and discussions that have appeared on this subject. However, we have included in the reference list the more important ones known to us.

The nature of tuberculosis dictates that any conclusive statement about it must be based on a period of observation long enough to include its entire evolution, which is the span of life. Therefore, the only way to determine the seriousness of the problem with any degree of accuracy is to start with the students as they enter the school of medicine and follow them carefully throughout life. This is a relatively simple matter as long as they are students, interns, and resident physicians in hospitals but it becomes a difficult matter to keep in touch with all of them after they locate in various parts of the world. Some will neglect or refuse to answer questionnaires, because of fear of publicity. Indeed, the physician who develops tuberculosis usually does not want any one to know about it except his personal physician.

We have attempted to trace the 1,894 students who graduated or were scheduled to graduate from the school of medicine of the University of Minnesota from 1919 to 1936 inclusive. Group I includes 1,441 students who were in the graduating classes from 1919 to 1932 inclusive, and Group II includes the 453 students who were in the classes graduating from 1933 to 1936. Prior to 1929, when the class graduating in 1933 entered the university, no special routine examinations for tuberculosis were made, consequently our information on Group I was obtained largely through questionnaires. Although we knew of the majority of students who fell ill from tuberculosis while in school, as well as those who had since fallen ill, the questionnaires added more cases to this list. While the response to our questionnaires was a manifestation of splendid coöperation on the part of the former graduates of this school of medicine, we were unable to secure information concerning 7.5 per cent of this group. The carefully outlined program of examinations for tuberculosis among our medical students since 1929 has provided us with information on infection attack rate, appearance of lesions by roentgen-ray film, symptoms, etc. in Group II.

In the classes of 1919 to 1936, we know of 35 deaths from causes other than tuberculosis. Of the remaining 1,859, 90 per cent replied to the questionnaire. In Group I, the leading non-tuberculous illness reported was pneumonia with 42 cases; this was followed by 28 cases of appendicitis, and 13 cases of scarlet fever. In all, 242 individuals reported serious illness from a total of 68 different disease entities. In Group II, of the 369 who replied to our inquiries, 49 have had major non-tuberculous illnesses caused by 28 disease entities. In this group also, pneumonia, appendicitis and scarlet fever were the leading causes of these illnesses.

GROUP I

The total number of replies from the members of the classes of 1919 to 1932 was 1,304. All deaths from tuberculosis are included in this number.

In the letters sent to this group, the following questions were asked:

1. Did you suffer from pleurisy with effusion or tuberculosis in any form while in school?
2. Have you had any form of tuberculosis since graduation?
3. Do you know of other members of your class who have been ill from, or have died of tuberculosis in school or since graduation?
4. Do you react to the tuberculin test? If so, how long have you been a reactor?
5. Have you had a roentgen-ray film examination of your chest recently? If so, did it reveal any abnormal shadows?
6. Have you had any other serious illness since graduation?

Forty-one (3.14 per cent) stated that they developed clinical tuberculosis while in school. Ten others reported having had pleural effusions as students and five others stated that they had tuberculosis before entering medical school. Thus, 51 (3.91 per cent) of this group developed clinical tuberculosis, including pleurisy with effusion, during their years in medical school before graduation.

Eliminating the five individuals who developed clinical tuberculosis prior to entering medical school and the 51 others who developed tuberculosis while in school, 41 of the remaining 1,248 graduates (3.29 per cent) including four cases of pleural effusion, reported that they developed tuberculosis after graduation from medical school.

Exclusive of the five developing tuberculosis before entering medical school, 92 (7.07 per cent) have had clinical disease while in school or since graduation. Of these, 11 (0.85 per cent) have died of tuberculosis.

Concerning tuberculin reactions, 389, or 29.9 per cent, have either had no tests or do not remember the results. Of the remaining 915 reporting, 655, or 71.6 per cent, stated that they had positive reactions to tuberculin while 260, or 28.4 per cent, reported negative reactions. The 655 positive reactions were broken down according to the time at which they were acquired. Two hundred and thirty-four (35.7 per cent) did not know when they became reactors. Eleven were dead, of whom one replied before death. Of the remaining 411 reactors, 140 (34.0 per cent) became positive before entering the medical school; 207 (50.4 per cent) became reactors while in medical school; and 64 (15.6 per cent) became reactors after graduation.

The percentage of persons recorded as reactors to tuberculin varied from 15 to 33 until 1925, whereas the percentage of graduates who either had no tests or did not remember ran from 46 to 62 during this same period. In 1925 a tuberculosis service was made compulsory and in 1929 routine annual testing of all medical students was begun. The number reporting reactions had risen sharply since that time while the number who have not been tested or do not remember has shown a correspondingly sharp decrease. The 1932 class recorded 85 per cent reactors and only 3 per cent no test (table 1).

TABLE I
Summary of Data Obtained by Questionnaire for Group I

Year	Number of Graduates	Dead (non-tuberculous)	Total Replies	Dead of Tuberculosis	Tuberculosis in School	Tuberculosis Since School	Tuberculin Reaction						Number Having Recent Chest Examination
							Non-reactors	No Test	Became Reactors				
									Before School	In School	After School	Unknown	
1919	59	1	55		2	2	0	4	5	14	30	25	
1920	92	5	79	3	4	4	5	0	5	17	37	32	
1921	81	1	73		3	1	1	4	5	7	41	32	
1922	76	3	69		3	2	2	0	2	6	43	30	
1923	78	4	69		2	0	1	2	4	15	33	35	
1924	102	3	92	3	3	6	2	6	5	18	41	51	
1925	90	2	79		5	0	6	6	0	15	37	40	
1926	107	5	96	1	5	2	3	5	5	27	29	53	
1927	103	1	95	1	6	4	7	9	4	26	32	46	
1928	120	1	109		3	2	8	18	4	27	24	57	
1929	134	2	120	1	2	3	11	27	8	26	14	69	
1930	126	0	114		3	8	29	32	8	17	9	69	
1931	129	2	118	2	5	4	24	41	3	20	15	74	
1932	144	1	136		5	3	39	57	7	13	4	96	
Total	1441	31	1304	11	51	41	140	207	64	234	260	389	709

We also were interested in determining as far as possible the time at which these physicians became reactors. The percentage that did not know this time ran close to 60 until 1926; since then it has declined steadily.

Seven hundred and nine (55 per cent) of those who replied reported that they had recent roentgen-ray examinations of the chest. The data show a steady increase over the years in the proportion of graduates having regular chest examinations including roentgen-ray films. In the 1919 class this percentage was 45 while in the 1932 class it was 70.

The total 92 individuals in Group I who reported having had clinical tuberculosis in some form approximates an entire class of our school of medicine. The eleven who died represent 26.2 per cent of the total number of deaths from all causes.

GROUP II

The 453 students who entered the School of Medicine from 1929 to 1932 inclusive, that is, in the classes graduating from 1933 to 1936 inclusive, were carefully examined throughout their enrollment in the School of Medicine. All the members of the class entering in 1929 were tested with tuberculin and all had roentgen-ray films of the chest annually regardless of the tuberculin reaction. The non-reactors on entrance were retested annually unless they became reactors. The members of the other three classes had the tuberculin test administered on entrance and annually or more often thereafter as long as they were non-reactors. In these classes roentgen-ray films of the chest were made only of the tuberculin reactors on entrance and annually thereafter and those who became reactors under our observation and annually thereafter unless shadows appeared, following which films were made more frequently. Four of the 453 have died of non-tuberculous conditions. The remaining 449 are included in this report.

Table 2 shows that in these classes on entrance the percentage of reactors to tuberculin ranges from 33.3 to 37, while on graduation the range is from 57.7 to 77.9 per cent. The average in the four classes, table 3, is 35.6 per cent on entrance to the School of Medicine, 41 per cent at the end of the third year, and 67 per cent at the end of the fourth year, and 50.2 per cent of those who reacted negatively to tuberculin upon entrance to the medical school became positive before graduation.

In figure 1, we have illustrated graphically the percentage of tuberculin reactors among medical students over the four-year period, while in figure 2 we have shown the total percentage of reactors on entrance, at the end of the third year, and on graduation. While there was an increase of reactors between entrance and the end of the junior year, it was greater during the senior year when the students had more contact with tuberculous patients. Of the 449 students in this group, 160 (35.6 per cent) reacted to the test on entrance, 145 (32.3 per cent) became reactors while in school, and 144 (32.1 per cent) were non-reactors on graduation.

The questionnaire sent to those who were recorded as reactors on graduation included this question: "Our records show that you reacted to the tuberculin test on graduation. Is this correct?" That sent to those who were recorded as non-reactors on graduation included the following questions: "Our records show that you did not react to tuberculin during the senior year. Is this correct? If so, have you become a reactor since graduation? If so, when and under what circumstances?"

From these replies, we learned that some students had tuberculin tests administered in various clinics during the latter part of their senior year, which were not reported to the Health Service. Thirteen reported that they

TABLE II

Comparison of Percentages of Infected Medical Graduates during Course of Study: on Entrance, the End of the Third Year, and the End of the Fourth Year of Medical School, Shown by Classes.

Class Graduating Year	Total in Class	Reactors Entrance		Reactors End Third Year		Reactors End Fourth Year	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
1933	78	26	33.3	33	42.3	45	57.7
1934	127	47	37.0	52	40.9	79	62.2
1935	113	39	34.5	46	40.7	79	70.0
1936	131	48	36.6	53	40.5	102	77.9

TABLE III

Comparison of Percentages of Infected of 449 Medical Graduates during the Course of Study: on Entrance, the End of the Third Year, and the End of the Fourth Year of Medical School.

Number of Graduates	Reactors Entrance		Reactors End Third Year		Reactors End Fourth Year		Per Cent of Non-Reactors Who Became Reactors
	No.	Per Cent	No.	Per Cent	No.	Per Cent	
449	160	35.6	184	41.0	305	67.8	50.2

were definite reactors on graduation, which we had recorded as non-reactors, and 10 reported that they are definitely non-reactors, while our records show one mild reaction in each case. Since no subsequent reaction occurred in these 10 physicians, it is probable that our interpreters had over-read the tests. In each case we have accepted the statement of the graduate concerned. On this basis, 305 (67.9 per cent) graduated as reactors and 144 (32.1 per cent) as non-reactors.

Replies have been received from 369 of the 449 graduates in this group. Of these 102 were from physicians who did not react to tuberculin at the end of the senior year. Sixty-five of these have had tuberculin tests since graduation, among whom 30 (46.2 per cent) became reactors as interns, 15 (23.0 per cent) became reactors following their internships, 20 (30.8 per cent) are still non-reactors.

Although few of these graduates took internships in hospitals which required tuberculosis services, practically all were in hospitals where they were exposed to the unsuspected contagious case of tuberculosis admitted for some other co-existing condition. Moreover, most of these hospitals do not examine the members of their own personnel. Certainly to allow 46.2 per cent of uninfected interns to become infected during their hospital services constitutes a serious problem in tuberculosis control. From our own observations among these physicians while they were students, together with

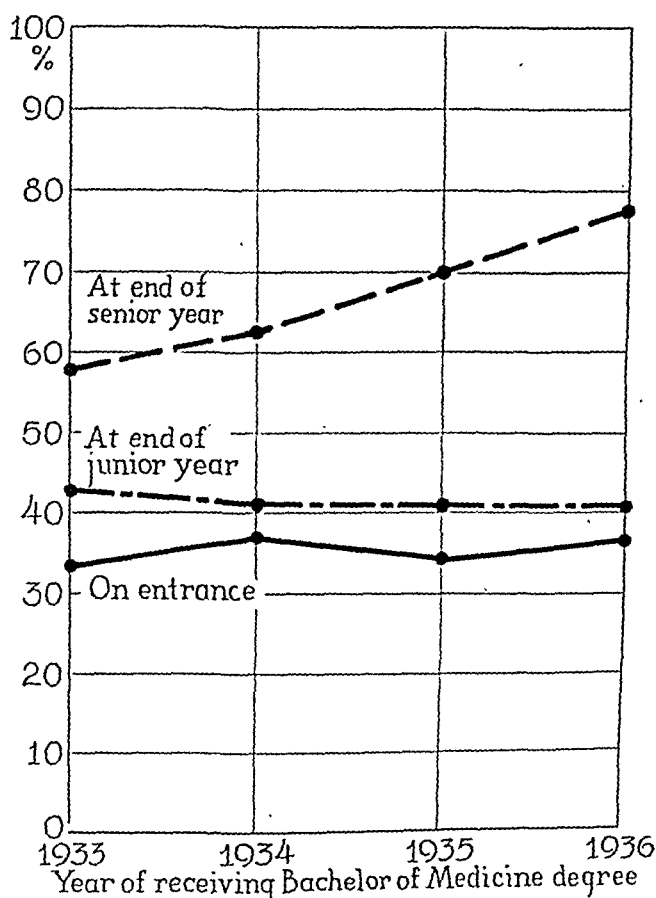


FIG. 1. Percentage of positive tuberculin reactors among medical students.

their replies to our questionnaires, we now know of a total of 350 (78.2 per cent) who are reactors to tuberculin.

Students in the College of Education, the control group, came from the same general section of the country and while in school lived in the same general environment as the students of medicine except that they were not brought in direct contact with tuberculous patients as a part of their work. On entrance to the College of Education 24.8 per cent of the students reacted to tuberculin, while on graduation 28.5 per cent reacted (figure 2). Thus, only slightly more than 1 per cent of the non-reactors became infected each year. Apparently in this community the infection attack rate is only about

1 per cent per year, as indicated by the findings in this group of students in the College of Education and the work of Stewart on children.

The following questions were included in our questionnaire:

"Have you had pleurisy with effusion or tuberculosis in any form, since graduation? Have you had roentgen-ray film examination of your chest recently? If so, did it reveal any abnormal shadow? Have you had any other serious illness since graduation? Do you know of any other members of your class who have been ill from or have died of tuberculosis, either in

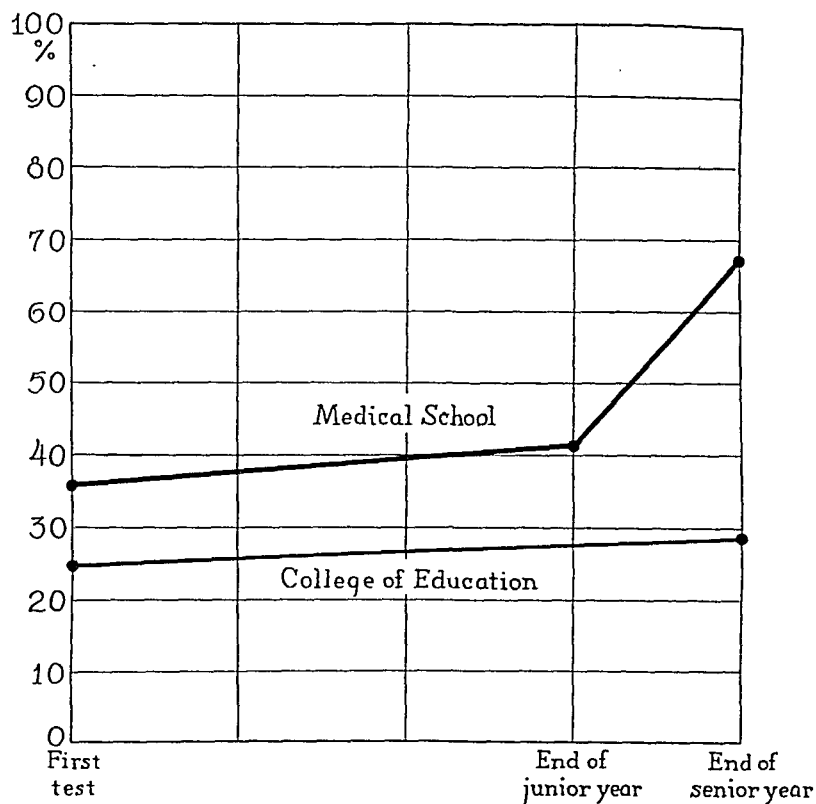


FIG. 2. Percentage of positive tuberculin reactors among students over four year period.

school or since graduation?" Three hundred and sixty-nine (82.2 per cent) of the graduates of these four classes replied and 291 (78.9 per cent) of those who had reacted to tuberculin have had recent roentgen-ray examinations of their chests.

GROUP II STUDENTS WHO DEVELOPED PRIMARY TUBERCULOSIS COMPLEXES BEFORE ENTERING MEDICAL SCHOOL

On entrance to the school of medicine there were 160 students in the classes of 1933-36 inclusive who had already developed primary complexes as manifested by the tuberculin reaction.

A. Those Who Had New Lesions Demonstrated while in School

In the fall of 1929 this student entered the school of medicine as a tuberculin reactor. In January 1930 films of his chest were clear. In March 1930, he had an effusion in the right pleural cavity but no evidence of disease could be seen in either lung. In February 1935, definite disease was demonstrated in both upper lobes. In February 1936, the disease in the right lung had increased but we have been unable to locate him since that date.

This student entered medical school in 1932 as a tuberculin reactor. There was evidence of a primary complex in the right lung and diaphragmatic adhesions on the right side. In 1933 he had renal tuberculosis and tuberculous epididymitis on the left side; these were treated surgically in 1934. In May 1936 he had pleural effusion on the left side. This physician is now practicing medicine.

B. Those Who Had New Lesions Demonstrated since Graduation

In the fall of 1929, when this student entered the medical school he was a reactor to tuberculin. In January 1930 there was evidence of calcium deposits in both hilum regions. In the spring of 1936 while practicing medicine, he had a pulmonary hemorrhage and a definite area of disease was found in the right upper lobe. He was in a sanatorium approximately six months, following which he remained inactive at home. The roentgen-ray shadow diminished definitely in size and he returned to work in the spring of 1937. At present he is practicing medicine.

In the fall of 1932, on entrance to the medical school, this student reacted to tuberculin. Roentgen-ray films of the chest throughout his medical course were clear. In February 1937 he developed pleurisy with effusion on the right side. Although this was diagnosed clinically as tuberculosis, tubercle bacilli were not recovered from the fluid.

In the fall of 1932, this student of 28 years entered the School of Medicine as a tuberculin reactor. Roentgen-ray films of his chest revealed evidence of a primary complex in the left lung and hilum. He completed his internship in 1936 with no change in the roentgen-ray film examination and with no symptoms of tuberculosis. He then entered the practice of medicine and was apparently healthy until December 1938, when he had an attack of bronchitis and complained of fatigue. On January 6, 1939, a roentgen-ray film was made of his chest which revealed definite evidence of disease involving the greater part of the upper half of the right lung in addition to the evidence of the primary complex in the left lung hilum. He was admitted to a sanatorium, where he is now being treated by artificial pneumothorax.

Thus, among 160 students who had primary tuberculosis complexes in their bodies on entrance to the school of medicine, we know of five (3.1 per cent) who have had diagnoses of clinical tuberculosis (table 4).

TABLE IV

School of Medicine

160 with primary complex on entrance		
a. Lesions detected while in school,	2	} (3.1 per cent)
b. Lesions after graduation,	3	
145 developed primary complex in school		
a. Lesions detected while in school,	11	} (9.6 per cent)
b. Lesions after graduation,	3	
45 developed primary complex after graduation		
Lesions detected,	5	

School of Education

686 reactors	
Lesions detected while in school,	3 (0.44 per cent)

GROUP II STUDENTS WHO DEVELOPED PRIMARY TUBERCULOSIS COMPLEXES WHILE IN SCHOOL

One hundred and forty-five students in Group II developed the primary tuberculosis complex as manifested by the tuberculin reaction while in school. In some of these cases the location of lesions became demonstrable before or after graduation.

A. Those Who Had New Lesions Demonstrated while in School

In the fall of 1929 this student was a non-reactor to tuberculin. She became a reactor in the spring of 1936. All films previously made of the chest were clear. In May 1936 a definite shadow appeared in the left second interspace. This slowly decreased and disappeared within approximately a year. We consider this lesion a primary focus. In the fall of 1938 she was employed as a resident physician in pediatrics.

In September 1929 as a freshman in the school of medicine this student was a non-reactor to tuberculin. He was found to be a reactor in August 1934. All roentgen-ray films prior to June 1934 were clear. During this month, however, there was evidence of disease at the level of the first interspace on the left side. Films in August 1935 revealed a decrease in the extent of the shadow. He was apparently well in 1938. We believe the lesion demonstrated by roentgen-ray film was only a part of a primary tuberculosis complex.

This student of medicine entered the freshman class in the fall of 1928 as a non-reactor to tuberculin. Roentgen-ray film of his chest in 1930 was clear. In June 1931, there was evidence of disease in the apex and first interspace of the right lung and in the first and second interspaces of the left lung. Films in February 1932, revealed no change in the shadows but in September 1934 and June 1935 the shadows had almost completely disappeared. He did not graduate until 1934. Since that time he has led an active life and is now practicing medicine. Apparently the lesions demonstrated by roentgen-ray film were only primary foci.

In the fall of 1930, this pre-medical student was a non-reactor to tuberculin. In February 1935 he was found to be a reactor. The same month an area of disease was revealed by roentgen-ray film at the level of the right third interspace near the periphery. In May 1935 the shadow had slightly increased in extent. In June it had decreased. In October and November 1935 and in January 1936 it remained unchanged. Later he had an interpretation of a small cavity by a roentgen-ray worker in another state. Artificial pneumothorax was instituted and he is still on that treatment. At no time have there been symptoms. In reviewing the case there is considerable doubt in our minds whether a significant cavity actually existed; or, if so, whether it represented anything more than a small cavity which one occasionally sees in a primary focus after the caseous center is eliminated through the bronchial tree. Usually these are of no clinical significance and disappear rather promptly as far as one can determine from roentgen-ray examination. Therefore, we are of the opinion that the lesion demonstrable by roentgen-ray film was a primary focus.

In the fall of 1929 as a freshman in the school of medicine, this student was a non-reactor to tuberculin. In February 1933 he was found to be a reactor. All films were clear until that time, when a small but definite area of disease was present at the level of the right fourth interspace. We consider this lesion as a primary focus. In October 1933 while serving as an intern, fluid accumulated in the right pleural cavity. This we regard as a reinfection form of tuberculosis dependent for its development on allergy and bacilli from a primary complex. In November 1934, there was definite evidence of a reinfection type of lesion in the apex of the right lung. In

January 1935 pulmonary hemorrhage occurred and tubercle bacilli were present in the sputum. Temporary interruption of the phrenic nerve has since been performed three times and he spent more than one year in bed. At present the shadow in the right apex has practically disappeared and he is practicing his profession.

In February 1930 as a freshman in the medical school, this student was a non-reactor to tuberculin. In February 1931 he reacted to the tuberculin test. Roentgen-ray films were clear. In May 1931, fluid was present in the right pleural cavity and a small area of disease was seen at the level of the third interspace in the right lung which we interpreted as representing the primary focus. After three months in bed, the fluid had disappeared. The shadow in the right third interspace remained unchanged through April 1933. He is now practicing medicine.

In February 1930 as a freshman in the school of medicine, this student was a non-reactor to tuberculin. Periodic tests revealed no reaction until after a tuberculosis service in the fall of 1932. In February 1933, effusion was present in the right pleural cavity. This had completely disappeared by June 1933. In August 1933, a small shadow was detected at the level of the right second interspace. This was still present and unchanged in June 1937 and August 1938. We have regarded this lesion as a primary focus. At present she is practicing her profession.

In March 1933 as a sophomore in the school of medicine, this student was a non-reactor to tuberculin. Periodic tuberculin tests resulted in no reaction until May 1935 when he was found to have fluid in the left pleural cavity. There was no evidence of effusion in August 1935. Roentgen-ray films of the chest have since been clear except for evidence of slight thickening of the pleura on the left side. The last examination was in April 1938. He is now practicing his profession.

In the spring of 1930, this pre-medical student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until June 1933. All roentgen-ray films of the chest were clear until December 1934 when he had an effusion in the right pleural cavity. After several months the fluid disappeared. There is now no evidence of disease revealed by roentgen-ray film. He is practicing his profession.

In the fall of 1930, this pre-medical student was a non-reactor to tuberculin. In April 1933, he was found to be a reactor. In the summer of 1933 and the winter of 1934 films of the chest were clear. In February 1935, there was definite evidence of disease in the right subclavicular region. Periodic films over the next several months revealed no change. In October 1936, while serving as an intern there was possible roentgen-ray evidence of a small cavity in the area of disease. Because of the duration of time between the tuberculin reaction and the appearance of shadow we are of the opinion that this lesion represents the reinfection form of tuberculosis. Artificial pneumothorax was instituted and strict bed rest was employed for six months. There were no symptoms at any time. He is now working on a full-time basis.

As a freshman in the school of medicine in January 1932, this student was a non-reactor to tuberculin. Periodic tests revealed no reaction until February 1935. During the previous month he had spent two weeks on a tuberculosis service. Six weeks after leaving the service he developed fever and malaise. After having a fever of 102° to 104° for three weeks, erythema nodosum appeared. In November 1935, while he was an intern he developed pain over the right third costo-chondral junction, followed by a tumor mass in this region. Aspirated pus inoculated into guinea pigs resulted in tuberculosis. Two and one-half months later, he had curettement of the tuberculous chondritis. In March 1936, he experienced pain in the lumbar region. Roentgen-ray film of the lumbar spine revealed no evidence of disease. In July 1936, he complained of night sweats and fatigue. Examination revealed evidence of a left psoas abscess which was aspirated. He entered a sanatorium where the psoas abscess was aspirated several times. In January 1937, an abscess developed over the crest of the right ileum which drained spontaneously both posteriorly and laterally. In Decem-

ber 1938, there was still a small amount of drainage from the sinuses in the left inguinal region, the right iliac crest, and the right fifth lumbar region. At no time has there been any evidence of pulmonary tuberculosis. He resumed his internship in the fall of 1938.

B. Those Who Had New Lesions Demonstrated after Graduation

In 1930, this pre-medical student was a non-reactor to tuberculin. Periodic tests revealed no reaction until January 1933. All roentgen-ray films of the chest were clear through March 1935. In July 1935, pleural effusion was present on the left side. In November 1935, the fluid had completely disappeared. He is now apparently in good health and is practicing medicine.

In the spring of 1932, as a freshman in the school of medicine, this student was a non-reactor to tuberculin. Periodic tests revealed no reaction until November 1934. All roentgen-ray films through March 1935 were clear. In July 1935, he had a pulmonary hemorrhage while serving his internship. Roentgen-ray films revealed definite evidence of disease in the medial portion of the right upper lobe. Strict bed rest and artificial pneumothorax were instituted. He has continued on artificial pneumothorax and is now working full time as a physician.

In 1931 this pre-medical student was a non-reactor to tuberculin. Periodic tests revealed no reaction until December 1934. All roentgen-ray films of the chest throughout his medical course were clear. While practicing medicine in the spring of 1938, he was found to have pulmonary tuberculosis with cavitation involving the right lung. Tubercle bacilli were recovered from the sputum. Artificial pneumothorax was instituted and has been continued. He is now working on a part-time basis.

Thus, of 145 students who developed primary tuberculosis complexes under our observation, we know of 14 (9.6 per cent) who have had the location of the lesions demonstrated (tables 4 and 5). Attention must be

TABLE V

School of Medicine

145 developed primary complexes in school
14 (9.6 per cent) location of lesions detected
4 (2.75 per cent) primary foci only
5 (3.44 per cent) pleurisy with effusion only
1 (0.69 per cent) extrapulmonary lesions
4 (2.75 per cent) clinical pulmonary lesions

School of Education

686 reactors
3 (0.44 per cent) location of lesions detected
1 (0.15 per cent) primary focus only
2 (0.29 per cent) clinical lesions

called to the fact, however, that four (2.75 per cent) had evidence only of primary foci located by roentgen-ray film; five (3.44 per cent) had only pleurisy with effusion; one (0.69 per cent) developed extrapulmonary clinical tuberculosis; and four (2.75 per cent) developed clinical pulmonary disease. The remaining 131 would not have known of the presence of tuberculosis in their bodies had it not been for the routine periodic tuberculin test. In the entire group of 145, there has not been a case of meningitis, miliary disease, or tuberculous pneumonia.

In this study we have omitted a few questionable parenchymal lesions as we see no justification to include anything so indefinite as questionable

roentgen-ray findings. Moreover, we have omitted those with evidence of enlargement of the hilum shadows, since these are by no means always diagnostic tuberculous lesions.

Among the 45 students who replied to our questionnaire and stated that they had become tuberculin reactors since graduation, the following have shown evidence of lesions by roentgen-ray film examination:

As a freshman in the school of medicine in the fall of 1929 this student was a non-reactor to tuberculin. Periodic tests revealed no reaction throughout his medical course. Roentgen-ray films of the chest were clear. In 1935 while serving as an intern he was found to be a reactor. Roentgen-ray films of his chest revealed evidence of a lesion which proved to be due to a primary focus. This resolved so films of his chest were clear in 1937.

In the fall of 1929 this pre-medical student was a non-reactor to tuberculin. Periodic tests revealed no reaction throughout his course in medicine. All roentgen-ray films of his chest were clear. He became a reactor as an intern in 1934. In 1935 a shadow appeared in one lung which was interpreted as representing a primary focus. This had completely disappeared in 1938.

As a freshman in the school of medicine in the fall of 1930, this student was a non-reactor to tuberculin. Periodic tuberculin tests throughout his medical school course revealed no reaction. Roentgen-ray films of his chest were clear while in school. He became a reactor during the intern year. In February 1935 a lesion was detected at the level of the left second interspace. This was present through July 1935. In June 1938 the shadow could not be visualized on the roentgen-ray film.

As a freshman in the school of medicine in the fall of 1931, this student was a non-reactor to tuberculin. Periodic tests throughout his entire course in medicine revealed no reaction. Roentgen-ray films were clear. As an intern in 1934 he became a reactor. Roentgen-ray film examination revealed a shadow which was interpreted as representing a primary focus. The shadow later completely disappeared.

In the fall of 1931 as a freshman in the medical school this student was a non-reactor to tuberculin. All periodic tuberculin tests while in school revealed no reaction. Roentgen-ray films were clear throughout his medical school course. In 1935 (does not remember exact date) he was found to be a reactor to tuberculin. In the fall of 1935 while serving as an intern, a shadow appeared in the apex of the right lung. He was institutionalized for five months. No symptoms have been present at any time. Apparently the shadow represented a primary tuberculous focus.

Thus among 305 students of medicine who were tuberculin reactors when they entered the school of medicine or became reactors while in school, 18 (5.9 per cent) developed lesions which were located by roentgen-ray or other methods of examination (tables 4 and 5). Among the students in the College of Education on the campus of the University of Minnesota from 1932 to 1937, a total of 686 who reacted to tuberculin either on entrance to the college or subsequently had roentgen-ray film examination both on admission and just prior to graduation. Three (0.44 per cent) of these students developed lesions which were located by roentgen-ray film examination (tables 4 and 5). Neither in the School of Medicine nor the College of Education do we know of any who developed tuberculosis in the absence of a tuberculin reaction.

The findings of this study emphasize, in addition to the hazards of exposure, the fact that the entire span of life must be considered in every case

tuberculosis whether the diagnosis is made by the tuberculin test alone or by the demonstration of the actual location of lesions. In contrast to most diseases dealt with daily by the physician the immediate results may be negligible, but the remote results, as in syphilis, may be significant.

These students, we have seen the evolution of tuberculosis: the history of the disease, the first tuberculin reaction, occasional location by roentgen-ray of the primary focus, the reinfection type of lesions in the lungs, pleura, and elsewhere, the procedures carried out in Group II represent our future tuberculosis control since records of tuberculin reactions should be available for the present generation of school children when a question of diagnosis arises.

SUMMARY

In this study we have attempted to determine the tuberculosis situation among 1,441 persons who were in the University of Minnesota School of Medicine classes graduating from 1919 to 1932 inclusive (Group I). Of these, 11 have died from non-tuberculous conditions. Of the remainder, 92 per cent replied to our questionnaire or evidence of death from tuberculosis was obtained. In this group 7.1 per cent reported having had clinical tuberculosis including pleurisy with effusion, while in school or since graduation. This represents 92 individuals or approximately the number in the entire class. Eleven have died from tuberculosis.

Two hundred forty-two physicians reported having had serious non-tuberculous illnesses from 68 disease entities. The first three causes of death in order of numbers were pneumonia, appendicitis, and scarlet fever.

We have attempted to determine also the tuberculosis situation among members of four classes entering the school of medicine from 1929 to 1932 inclusive (Group II) and those graduating from 1933 to 1936 inclusive (Group II). These four classes include a total of 453 students, four of whom have died from non-tuberculous conditions. These students were studied by means of routine tuberculin tests, roentgen-ray films of the chest, and other indications of complete examinations. Questionnaires were sent to all of the graduates of these classes.

In Group I, 42 deaths have occurred, 11 of which were from tuberculosis. In Group II, there were four deaths, none of which was from tuberculosis. Hence, in the total group of 1,894 graduates from the Medical School from 1919 to 1936, there have been 46 deaths, 23.9 per cent of which were due to tuberculosis.

On entrance to the School of Medicine, 35.6 per cent of the members of our classes in Group II were reactors to tuberculin. On graduation, this proportion had increased to 68 per cent. Sixty-five who graduated as non-reactors to tuberculin have had subsequent tuberculin tests. Of these,

46.2 per cent had become reactors as interns and 31.1 per cent following internships. We now know of 78 per cent of the graduates of these four classes who are reactors to tuberculin.

6. In the College of Education of the University of Minnesota, 24.8 per cent of one class of students reacted to tuberculin on entrance and only 28.5 per cent of these same students reacted on graduation.

7. Among 160 students who already had primary tuberculosis complexes on entrance to the School of Medicine, two developed clinical tuberculosis while in school and three after graduation.

8. Of the 145 students who developed the primary tuberculosis complex while in school, 11 developed demonstrable lesions as students and three after graduation. Of these 14 students, four had only primary foci demonstrated by roentgen-ray film; one had clinical extrapulmonary tuberculosis; five had pleurisy with effusion; and four had chronic clinical pulmonary disease.

9. Of the students who developed primary complexes after graduation, as manifested by the tuberculin reaction, we know of five who had lesions in such locations as to be visualized by roentgen-ray film examination. All of these apparently were primary foci.

10. Among the students in Group II we have not learned of a case of tuberculous meningitis, miliary tuberculosis or so-called "infantile" tuberculosis.

11. In this entire study we know of no student with tuberculosis who did not react to the tuberculin test.

BIBLIOGRAPHY

- ARMSTRONG, JOHN: Practical illustrations of the scarlet fever, measles, pulmonary consumption and chronic diseases, London, 1818, pages 223 and 246.
- BATES, ROBERT R.: A follow-up study of the medical-student and physician patients discharged from Trudeau Sanatorium, 1916-1931, *Am. Rev. Tuberc.*, 1935, xxxii, 161.
- BRUETSCH, WALTER L.: Eighty-fourth annual report of the Board of Trustees and Superintendent of the Central State Hospital, Indianapolis, Indiana, for the Fiscal Year Ending September 30, 1932.
- CHADWICK, HENRY D.: Tuberculosis as it affects the general hospital, *Bull. Am. Hosp. Assoc.*, April, 1934.
- DIEHL, H. S., and MYERS, J. A.: Tuberculosis in college students, *Trans. Nat. Tuberc. Assoc.*, 1936, p. 163.
- DIEHL, H. S.: Tuberculosis control in University of Minnesota Students, *Journal-Lancet*, 1932, lii, 224.
- FITZ, R.: The problem of pulmonary tuberculosis in medical students, *Jr. Am. Med. Assoc.*, 1931, xcvi, 2063.
- FITZ, R.: The problem of pulmonary tuberculosis in medical students, *Trans. Assoc. Am. Phys.*, 1931, xlv, 241.
- FORD, W. W.: Discussion of Fitz's paper, *Jr. Am. Med. Assoc.*, 1931, xcvi, 2064.
- GORDON, B., and CASHMAN, W. M.: Tuberculosis in workers after residence in a tuberculosis hospital, *Jr. Am. Med. Assoc.*, 1930, p. 1643.
- HARVEY, B. C. H.: Discussion of Pepper's paper, *Jr. Assoc. Am. Med. Coll.*, 1932, vii, 9.

- HERMAN, N. B., BAETJER, F. H., and DOULL, J. A.: Tuberculous infection in medical students, *Bull. Johns Hopkins Hosp.*, 1932, li, 41.
- HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., and OPIE, E. L.: Tuberculosis in medical and college students, *Arch. Int. Med.*, 1931, xlviii, 734.
- HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., and OPIE, E. L.: Tuberculosis in medical students, *Trans. Assoc. Am. Phys.*, 1931, xlv, 237.
- HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., and OPIE, E. L.: Further study of tuberculosis among medical and other university students, *Arch. Int. Med.*, 1935, lv, 709.
- JACOB, P.: Discussion of paper by Scheel, *Bull. Internat. Union Against Tuberculosis*, 1937, xiv, 512.
- JENNINGS, FRANK L.: Tuberculous infection and morbidity among medical students and physicians, *Minn. Med.*, 1938, xxi, 102.
- KIRCHNER, M.: Tuberkuloseerkrankungen und -todesfälle bei Ärzten und dem Pflegepersonal und die Frage der Dienstbeschädigung, *Ztschr. f. Tuberk.*, 1925, xliii, 345.
- LEES, H. D.: Personal communication.
- LAIRD, A. T.: Clinical tuberculosis among employes of local institutions caring for tuberculosis patients, *Minn. Med.*, 1935, p. 452.
- MYERS, J. A., and WULFF, MARJORIE: Eleven years' observations on tuberculosis among university students, *Am. Rev. Tuberc.*, 1932, xxvi, 530.
- MYERS, J. ARTHUR: Types of tuberculous lesions found in the chests of students of nursing and medicine, *Am. Rev. Tuberc.*, 1933, xxviii, 93.
- MYERS, J. ARTHUR, DIEHL, H. S., BOYNTON, RUTH E., and TRACH, BENEDICT: Development of tuberculosis in adult life, *Arch. Int. Med.*, 1937, lix, 1.
- MYERS, J. ARTHUR: How shall we protect our students from tuberculosis? *Trained Nurse and Hosp. Rev.*, 1934, xcii, 332.
- MYERS, J. ARTHUR, DIEHL, H. S., LEES, H. D., and LEVINE, IDA: The evolution of tuberculosis in students of nursing and medicine, *Trans. Nat. Tuberc. Assoc.*, 1934, p. 345.
- MYERS, J. ARTHUR: Are nurses and physicians protected against tuberculosis? *Trained Nurse and Hosp. Rev.*, 1933, xci, 416.
- MYERS, J. ARTHUR, TRACH, BENEDICT, DIEHL, HAROLD S., and BOYNTON, RUTH E.: Tuberculosis in medical and nursing hospital personnel, *ANN. INT. MED.*, 1938, xi, 2181.
- OPIE, E. L., LANDIS, H. R. M. et al.: Tuberculosis in medical students, *Jr. Am. Med. Assoc.*, 1931, xcvi, 2064.
- PEPPER, WILLIAM: Incidence of tuberculosis among medical students (Read at the 42nd annual meeting of the Assoc. American Medical Colleges held in New Orleans, Nov. 30, Dec. 1 and 2, 1932).
- PEPPER, WILLIAM: Incidence of tuberculosis among medical students, *Jr. Assoc. Am. Med. Coll.*, 1932, vii, 5.
- POLLOCK, W. C., and FORSEE, J. H.: Reinfection among tuberculoallergic doctors and nurses at Fitzsimons Hospital, *Am. Rev. Tuberc.*, 1935, xxxi, 203.
- POLLOCK, W. C., and FORSEE, J. H.: Tuberculosis among doctors and nurses at Fitzsimons General Hospital, *Military Surgeon*, 1934, lxxv, 17.
- RIGLER, LEO G., and EXNER, F. B.: The latent period in the roentgen diagnosis of pulmonary tuberculosis, *Jr. Am. Med. Assoc.*, 1934, cii, 1750.
- SAYE, M. L.: Foreign letters: Paris, examination of students for pulmonary tuberculosis, *Jr. Am. Med. Assoc.*, 1935, civ, 2009.
- SCHEEL, O.: La tuberculose parmi les étudiants en Médecine à Oslo et sa prévention par la vaccination au B.C.G., *Rev. de la tuberc.*, 1935, 5 serie, i, 529.
- SCHEEL, O.: La primo infection tuberculeuse de l'adolescent et de l'adulte, *Bull. Internat. Union Against Tuberc.*, 1937, xiv, 477.
- SOPER, W. B., and AMBERSON, J. BURNS: Pulmonary tuberculosis in young adults, particularly among medical students and nurses, *Trans. Congr. Am. Phys. and Surg.*, 1938, p. 17.

- SOPER, W. B., and WILSON, JULIUS L.: The detection of pulmonary tuberculosis in 3,000 students entering Yale University, *Am. Rev. Tuberc.*, 1932, xxvi, 548.
- STEIDL, J.: Tuberculosis among medical students, *Am. Rev. Tuberc.*, 1932, xxvi, 98.
- STEWART, C. A.: Periodic accrediting of households, *Am. Jr. Dis. Child.*, 1937, liv, 699.
- STEWART, C. A.: Primary tuberculous infection attack rates; observations for selected local population groups, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2204.
- TAPIA, MANUAL: Discussion of Scheel's paper, *Bull. Internat. Union Against Tuberc.*, 1937, xiv, 504.
- The Anti-Tuberculosis Crusade in Italy, Abstract, *Jr. Am. Med. Assoc.*, 1934, p. 472.
- VAUCHER and STRAUSS: Les examens de médecine préventive et la tuberculose chez les étudiants, *Rev. d'hyg.*, 1935, lvii, 506.
- WEBB, GERALD B.: Tuberculosis, 1936, Paul B. Hoeber, Inc., New York.
- WHITNEY, JESSAMINE S.: Death rates by occupation, Published by the National Tuberculosis Association, New York, 1934.

THE INTRAVENOUS USE OF SODIUM SULFAPYRIDINE IN THE TREATMENT OF LOBAR PNEUMONIA *

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THE intravenous use of sodium sulfapyridine was reported first by Marshall and Long.¹ Since the beginning of this study other reports^{2, 3} on the parenteral use of sodium sulfapyridine for special indications have appeared. In none of these reports has the drug been given routinely and repeatedly. Data obtained from the routine repeated intravenous infusion of sodium sulfapyridine should be valuable in establishing the indications for its use by this route.

MATERIAL AND PROCEDURE

This report presents our experience with the intravenous use of sodium sulfapyridine monohydrate in the treatment of 54 patients suffering with lobar pneumonia. The patients in this study were admitted to the Grady Memorial Hospital in Atlanta, Georgia, between December 15, 1939 and March 16, 1940.

Typing for pneumococci by the quellung reaction was attempted from sputum or a throat swab of every patient at the time of admission. In many cases we were unable to type the sputum even after several attempts. Blood for culture and for a complete blood count and a urine specimen was obtained before treatment was instituted. Blood counts and urinalyses were repeated daily early in the course of the illness. Serial roentgenograms of the chest were made in every case.

The diagnosis of lobar pneumonia was made from the history, physical findings, laboratory studies, serial roentgenograms and autopsy findings. The rather typical response to sulfapyridine was confirmatory evidence.

The routine dose of sodium sulfapyridine was 0.06 gram per kilogram of body weight. This amount of the drug was dissolved in 750 c.c. of physiological saline solution or 5 per cent dextrose solution. Saline was used when vomiting occurred; dextrose solution if there was no emesis. This dose of the drug was repeated every six hours until the temperature dropped to normal. Then the same amount was given every eight hours. After the temperature had remained normal for 48 hours, the same dose was injected every 12 hours. After a second 48 hour afebrile period the intravenous sodium sulfapyridine was discontinued and 1.0 or 0.5 gram of sulfa-

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From the Department of Medicine of Emory University School of Medicine, Atlanta, Ga.

Part of the sodium sulfapyridine was available through the courtesy of the Calco Chemical Co.

TABLE I

Case No.	Sex	Age	Type	Lobe	I. V. Sulfapyridine		Oral Sulfapyridine		Maximum blood level in mg. %	Anti-serum in 100,000 units	Day of Disease	Crisis in hrs. after start of drug	Day of discharge or death	Days of nausea and vomiting	
					Total Gm.	No. of Doses	Total Gm.	No. of Doses							
1	F	22	—	LL	63.0	21	83.0	105	33.3		13	36	30	2	
2	M	15	—	LL	63.0	18	15.0	43	57.4		3	48	16	1	
3	M	64	—	RU	104.0	26	28.0	24	16.6		4	L	25	2	
4	F	65	—	LL	63.0	21	8.0	8	8.7		2	24	19	2	
5	F	38	XIX	RU	35.0	10	40.5	60	8.0		4	24	18	8	
6	F	48	—	LL	21.0	6	34.0	34	12.9		3	24	30	1	
7	M	36	—	LL	8.0	2	83.5	123	5.7		5	L	33	4	
8	M	18	I	LL	41.0	15	—	—	10.5	1.0	2	36	20		
9	M	52	I	LU	66.5	19	23.5	47	8.0	2.0	4	48	21		
10	M	17	VII	RU	73.0	24	17.0	34	19.0		2	36	16	2	
11	F	37	—	RU	52.5	21	33.5	66	10.8	2.0	9	48	37	2	
12	F	47	XIV	LU	85.0	34	5.0	10	20.0		4	L	50	2	
13	F	36	I	LL	82.5	33	6.0	12	15.4		1	L	26	3	
14	M	13	V	LL	24.0	12	11.0	22	13.3		1	48	14		
15	M	34	VIII	LL	130.0	38	3.5	7	14.8	1.4	3	L	49	3	
16	M	64	—	RL	80.5	23	19.0	38	15.4		4	L	40	7	
17	F	19	V	RU	20.0	10	—	—	15.4	2.0	2	36	12	2	
18	M	26	—	LL	97.5	26	77.5	94	16.0		1	L	50	1	
19	M	65	III	LU	63.0	21	2.5	5	7.5		3	24	13	1	
20	M	38	I	RL	73.0	21	16.5	32	6.4		1	72	20	1	
21	M	56	III	RL	80.0	20	15.0	30	13.5		3	48	25	3	
22	F	24	IV	LL	51.0	17	15.0	30	11.8		6	36	13		
23	F	76	—	RL	42.5	17	20.5	41	22.2		4	48	19		
24	M	39	—	RU	64.0	18	7.0	13	23.5		3	48	18	1	
25	M	33	I	LU	52.5	15	31.5	63	23.5		1	36	46		
26	F	18	—	LL	40.0	20	21.5	42	9.5		5	24	20		

Delirious

Rash with drug fever, 9th day

Effusion

Hematuria

WBC 2,000 on admission

Irrational on admission

Rash- 14th day

Empyema with thoracotomy; alcoholism with DTs

Thrombosis

Irrational

Irrational on admission. Effusion, thrombosis, spread

11th day

Thrombosis

Irrational on admission

Thrombosis

Empyema

TABLE I—Continued

Case No.	Sex	Age	Type	Lobe	I. V. Sulfapyridine		Oral Sulfapyridine		Maximum blood level in mg. %	Anti-serum in 100,000 units	Day of Disease	Crisis in hrs. after start of drug	Day of discharge or death	Days of nausea and vomiting	
					Total Gm.	No. of Doses	Total Gm.	No. of Doses							
27	M	39	I	RU	42.5	17	1.0	1	33.3		2	60	26	7	Encephalopathy, 7th day; NPN 120, 8th day
28	F	18	I	LL	40.0	16	32.0	62	16.6		4	36	22	1	Effusion; thrombosis
29	F	15	I	RU	40.0	20	9.0	18	13.3		2	24	12		
30	F	33	I	RU	50.0	20	18.0	36	13.3		4	48	20		
31	M	14	V	LL	50.0	20	20.0	40	11.1		1	L	15	1	Thrombosis
32	M	37	VII	RM	15.0	5	—	—	10.0	2.2	1	48	14		Hemolytic anemia
33	M	18	I	RM	70.0	20	15.5	31	11.1		3	72	16	7	Thrombosis
34	M	29	I	LL	54.0	18	18.5	37	14.3		1	60	42	4	Irrational on admission; effusion
35	M	17	II	RL	22.5	9	27.5	47	7.1		1	36	15		Thrombosis
36	F	24	—	RL	42.5	17	23.0	27	6.7		2	48	20		
37	F	13	—	RL	16.0	8	9.0	17	12.5		1	36	11		
38	F	13	I	LL	6.0	3	—	—	3.5	2.0	1	48	18	1	Hematuria
39	M	23	IV	LL	60.0	20	11.0	22	12.5		1	36	16	5	Delirious on admission NPN 46
40	M	17	I	RU	27.0	9	—	—	20.8	2.0	1	36	19	4	Delirious on admission; thrombosis; NPN 100
41	F	54	—	RU	10.0	4	—	—	10.4		2	36	20		Hematuria
42	M	44	I	LL	54.0	18	12.5	25	9.1		1	72	12		Thrombosis
43	M	23	V	RM	45.0	15	21.0	42	6.2		2	36	13	1	Thrombosis
44	M	40	—	RM	54.0	18	19.0	38	6.6		?	36	36		Spread, 6th day
45	F	59	—	RU	15.0	6	—	—	6.6		1	36	23	1	Hemoglobinuria
46	F	25	—	LL	12.5	5	3.0	3	5.8		2	L	23		Hematuria on admission
47	M	52	XX	LL	56.0	12	—	—	25.0	1.0	?	—	6	3	Convulsions
48	M	49	XIV	RL	49.0	13	—	—	16.6	3.0	2	—	5	1	Irrational; effusion, anuria
49	F	64	—	LL	44.0	22	12.0R	6R	20.0		4	—	9	2	
50	M	55	I	RL	38.5	11	3.0R	1R	13.3	3.0	3	—	4		Irrational on admission. Empyema, hematuria, bacteremia
51	M	73	III	RU	32.5	9	—	—	26.7		?	—	3	1	
52	M	59	III	RM	24.0	7	—	—	4.0	2.0	3	—	6		Effusion
53	M	84	—	LU	16.0	5	—	—	—		2	—	5		
54	F	76	—	LL	13.0	6	—	—	25.0		4	—	2		
			—	RM			—	—							
			—	RL			—	—							

pyridine was given by mouth every four hours. An equal amount of sodium bicarbonate was given by mouth with each dose of sodium sulfapyridine or sulfapyridine. If the patient's response seemed unsatisfactory 48 hours after the parenteral injection of the drug was begun, type specific anti-serum was administered.

Just before all but the initial injections of the drug venous blood was withdrawn for a determination* of the amount of free sulfapyridine present. By obtaining the specimen before each injection we determined

TABLE II

	Group		Survivors		Fatalities	
	Aver.	Range	Aver.	Range	Aver.	Range
Intravenous Total Gm.	48	6-130	50	6-130	34	13-56
No. Doses	16	2-38	17	2-38	11	5-22
Oral Total Gm.	16	0-84	19	0-84	0	0
No. Doses	26	0-123	31	0-123	0	0
Maximum blood sulfapyridine mg. %	14.7	3.5-57.4	14.1	3.5-57.4	18.7	4.0-26.7
No. Hosp. Days	21	2-50	23	11-50	5	2-9

TABLE III

Days elapsing between onset and admission			
1 day	14 cases	5 days	2 cases
2 days	13 cases	6 days	1 case
3 days	9 cases	7+ days	2 cases
4 days	10 cases	unknown	3 cases

the lowest concentration of the drug in the blood. It is reasonable to suppose that higher concentrations were present in all of these patients during and shortly after the infusions.

Table 1 presents a summary of pertinent data for each of the 54 cases in this series.

In table 2 are shown the amounts of the drug given intravenously and orally. The average of the highest determination of free sulfapyridine in the blood in each case is given; the range of these values is also indicated. The number of hospital days is also given in average and range.

* *Blood*: Three c.c. of oxalated whole blood were measured into a flask and laked with 24 c.c. of 0.05 per cent aqueous solution of saponin, shaken and allowed to stand for 2 minutes. Three c.c. of 20 per cent trichloroacetic acid were added, shaken, and allowed to stand 1 minute, and then filtered. Ten c.c. of the filtrate were measured into a small flask and 1 c.c. of 0.1 per cent of freshly prepared sodium nitrate solution was added. This solution stood for 3 minutes and then there was added to it 5 c.c. of a solution of dimethyl- α -naphthalamine (1 c.c. of concentrated dimethyl- α -naphthalamine dissolved in 250 c.c. of 95 per cent ethyl alcohol). The resulting purplish-red azo dye was compared colorimetrically with a similarly treated standard.

Of the 54 patients studied 32 were males and 22 were females. The ages varied from 13 to 84 years. The average age of the whole group was 38 years; of the survivors 34 years; and of the fatalities 64 years. There were 22 patients aged less than 30 years; 23 between 30 and 59 years, and 9 patients aged 60 or more years. The number of days elapsing between the onset of the pneumonia and admission to the hospital is shown in table 3. The average elapsed time for the group was 2.84 days; for the survivors 2.82 days, and for the fatalities 3.0 days.

The incidence of the types of pneumococci in this series is shown in table 4. The lobe (or lobes) involved is shown in table 5.

TABLE IV

Type I.....	14 cases
Type II.....	1 case
Type III.....	4 cases
Type IV.....	2 cases
Type V.....	4 cases
Type VII.....	2 cases
Type VIII.....	1 case
Type XIV.....	2 cases
Type XIX.....	1 case
Type XX.....	1 case
Undetermined.....	22 cases

TABLE V

Lobe involved:		Combined:	
Left lower	20 cases	LL and LU	2 cases
Left upper	2 cases	LL and RU	2 cases
Right lower	9 cases	LL and RL	2 cases
Right upper	10 cases	LL, LU and RL	1 case
Right middle	3 cases	RM and RL	2 cases
Combined	10 cases	RM and RU	1 case
54 cases		10 cases	

RESPONSE

There were eight deaths (14.8 per cent mortality) in this group of 54 patients who were treated with sodium sulfapyridine intravenously.

Of the 54 patients, six (11.1 per cent) had a normal temperature within 24 hours after the drug was first administered. Sixteen (29.6 per cent) were afebrile within 36 hours; ten (18.5 per cent) within 48 hours; and five (9.3 per cent) within 72 hours. Of the 46 patients who recovered, nine (16.7 per cent of the 54) required longer than 72 hours to reach an afebrile state.

There was a spread of the pneumonic process in one fatal and two surviving cases. In the fatal case (number 47) the spread occurred after the drug had been discontinued because of tonic and clonic convulsions. The initial response of the infection was typical with crisis. Death was considered to be due to the toxic reaction from the drug.

The first surviving patient (number 1) had had an initial crisis within 36 hours and had been receiving 1.0 gram of sulfapyridine by mouth every four hours for six days. On the eleventh hospital day, while the free sulfapyridine in the blood was 3.3 mg. per cent, a spread of the pneumonia occurred. Sodium sulfapyridine was injected again but this time the response was by lysis.

The other surviving patient (number 18) was apparently well when the intravenous sodium sulfapyridine was stopped on the tenth hospital day. The free sulfapyridine content was 2.6 mg. per 100 c.c. of blood before the last injection. The oral administration of sulfapyridine was begun with 0.5 gram every four hours. The next day the blood level of free sulfapyridine was too low to read. The patient developed a pain over the contralateral lung, fever, and signs of consolidation. Sulfapyridine was increased to 1.0 gram every four hours and the patient recovered by lysis.

Administration of the drug was stopped on 11 surviving patients (numbers 6, 8, 13, 17, 27, 32, 38, 40, 41, 45, 46) because of hematuria, encephalopathy, rash or hemolytic anemia. Six of these recovered without further chemotherapy or specific anti-serum. The other five (numbers 8, 17, 32, 38, 40) were given type specific anti-serum the day the drug was stopped or the following day. While the drug was being continued, anti-serum was given to three patients (numbers 9, 12, 15); to one because of a very poor prognosis and to the other two because of leukopenia. The remaining four of the 12 patients who received anti-serum were in the fatal group.

BLOOD CELL CHANGES

The erythrocyte counts made on admission showed: more than 5 million erythrocytes in 6 cases; 4 to 5 million erythrocytes in 37 cases; 3 to 4 million erythrocytes in 10 cases; less than 3 million erythrocytes in 1 case.

During the course of the pneumonia, while frequent counts were being made, 15 cases showed a decrease of from 1 to 2 million erythrocytes per cu. mm. Five cases showed a decrease of more than 2 million below the admission count. Only one of these had acute hemolytic anemia. Transfusions of whole citrated blood were given to nine patients.

The leukocyte counts made on admission showed: more than 20,000 leukocytes in 23 cases; 10,000 to 20,000 leukocytes in 23 cases; 5,000 to 10,000 leukocytes in 6 cases; less than 5,000 leukocytes in 2 cases (2,000, 4,600).

Only two patients showed a subsequent decrease of leukocytes below 4,000 per cu. mm. Both had a low count of 3,900.

Only one positive blood culture (case number 50) was obtained.

BLOOD LEVELS

At the outset it was hoped that there would be some constancy in the free sulfapyridine levels in the blood. The variation of blood levels, how-

ever, with intravenous sodium sulfapyridine seemed almost as great as with oral sulfapyridine. In chart 1 is shown the great spread of the values for free sulfapyridine in the blood. All of these values were obtained while the

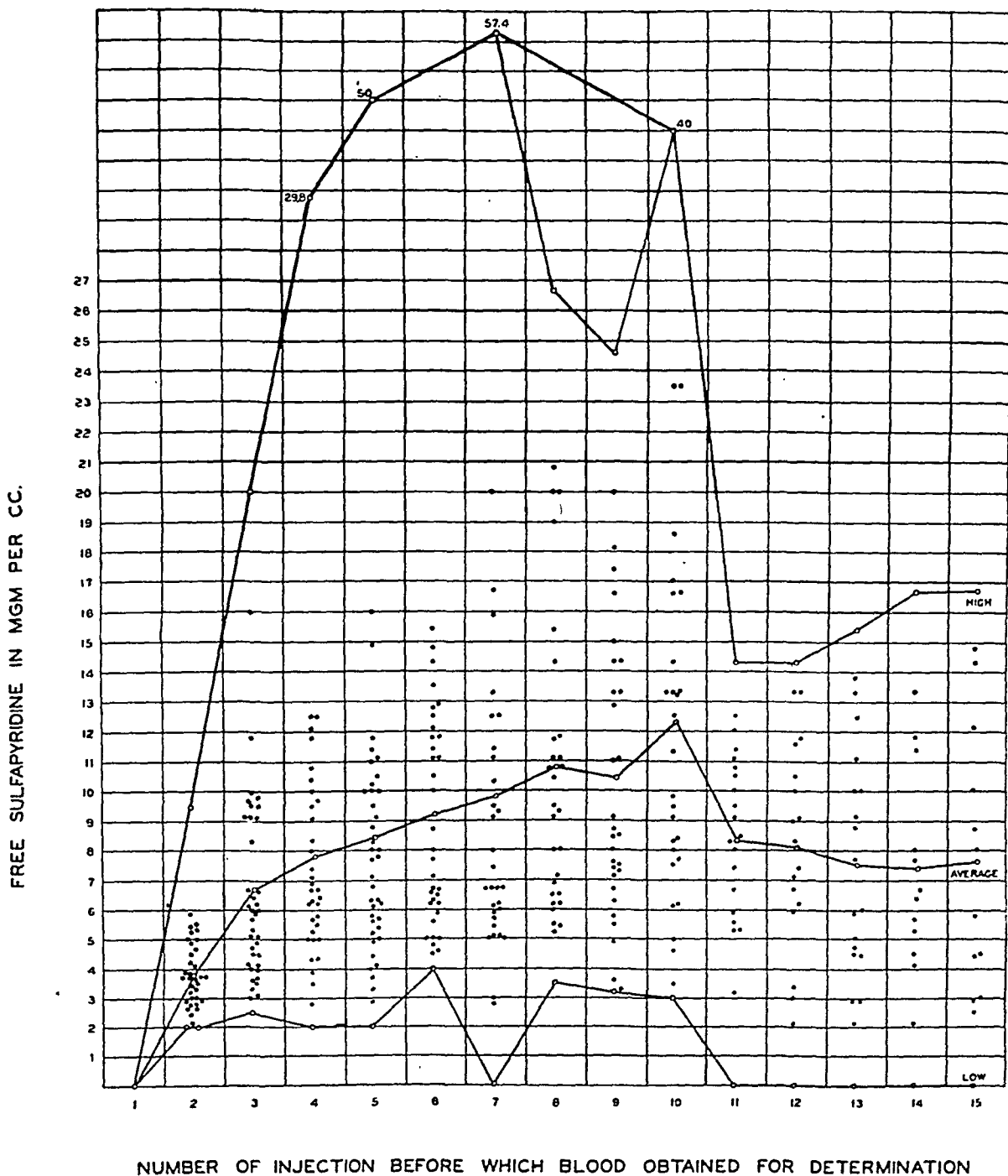


CHART 1. Levels of free sulfapyridine in the blood observed during the course of repeated intravenous injections of sodium sulfapyridine monohydrate.

patients were receiving the routine dose of sodium sulfapyridine every six or eight hours intravenously. The negative determination before the seventh injection was the last one in case number 52 which terminated fatally soon thereafter. The negative determinations which were obtained before the eleventh, twelfth, thirteenth, fourteenth and fifteenth infusions were all from the same case (number 36) which recovered without complications. The four readings above 27 mg. per cent on chart 1 occurred in the second patient treated. This patient, while receiving a 2 per cent solution of the drug, had marked nausea and vomiting which resulted in dehydration and the extremely high blood concentration. Following this experience, the drug was dissolved in 750 c.c. of saline or dextrose so that a patient getting an injection every six hours would have a daily fluid intake of at least 3000 c.c. Two surviving patients (numbers 1 and 27) had high blood levels of 33.3 mg. per cent after taking the drug orally (not shown on chart 1). Five patients (numbers 24, 25, 40, 51, 54) on chart 1 and four patients (numbers 12, 23, 47, 49) not on chart 1, had high concentrations between 20 and 30 mg. per cent. Of these nine, four were in the fatal group. We, as others,^{3,4,5} are impressed with the fact that high blood levels of free sulfapyridine seem no more effective than those of 3.0 to 4.0 mg. per cent.

The most marked variation in blood levels existed between different individuals. In the same person, however, there was often a rather marked variation while the same amount of drug was being injected at a regular interval. In chart 1 the curve representing the average level before each injection rises through the tenth injection. The subsequent fall would be expected, for by then most of the patients were receiving their injections every eight hours instead of every six hours.

In chart 1 is indicated the wide range in the blood level of free sulfapyridine that may be expected when a standard dose is administered intravenously. The data collected in this study are not sufficient to explain this variation. We regret that total as well as free sulfapyridine levels were not determined. As a result, we are unable to say how important a part is played by the rate at which sulfapyridine is acetylated. The charting of the fluid intake and output was not of sufficient accuracy to justify its use in determining the influence of the speed of urinary excretion on the blood level of the drug. These data do suggest that, after ingestion of sulfapyridine, differences in the rate and degree of absorption from the alimentary tract do not play as important a part in the variation of blood levels of free sulfapyridine as was originally supposed.

There was no unusual elevation of free sulfapyridine in the blood of six patients who developed hematuria:

Case 8 received 33 gm. in 72 hours. The highest concentration reached was 10.5 mg. per cent.

Case 38 received 6 gm. in 24 hours with a high concentration of 3.5 mg. per cent.

Case 41 received 10 gm. in 24 hours with a high concentration of 10.4 mg. per cent.

Case 45 received 15 gm. in 36 hours with a high concentration of 6.6 mg. per cent.

Case 46 received 12.5 gm. in 36 hours with a high concentration of 5.8 mg. per cent.

Case 50 received 31 gm. in 60 hours with a high concentration of 13.3 mg. per cent.

TOXIC REACTIONS TO DRUG

Nausea and vomiting occurred more frequently than any other toxic reaction. It was present in 31 cases, lasting from one to eight days with an average duration of 2.7 days. In no case was it severe enough to require stopping of the drug. The nausea and vomiting frequently began

TABLE VI

Case No.	High Blood Level	High Vomitus Level
16	13.3 mg. per cent	50.0 mg. per cent
33	11.1 mg. per cent	20.0 mg. per cent
39	8.0 mg. per cent	10.0 mg. per cent
18	16.0 mg. per cent	3.2 mg. per cent

TABLE VII

Reaction	No. Cases	Per Cent	Drug Stopped	Deaths
Nausea and vomiting	31	57.4	0	4
Encephalopathy	4	7.4	3	1
Rash	3	5.6	3	1
Hemolytic anemia	1	1.9	1	0
Granulopenia	0	0.0	0	0
Hematuria	6	11.1	6	1
Nitrogen retention	4	7.4	2	1
Anuria	1	1.9	0	1

about 15 minutes after the beginning of an injection, was most severe during the infusion and tended to subside following completion of the injection. With the first patients a 2 per cent solution was used. Nausea and vomiting were found to be more severe with the concentrated solution than with the drug dissolved in 750 c.c. of solution.

The vomitus of four patients was studied for its content of free sulfapyridine. In the vomitus of three of these, the concentration of free sulfapyridine was greater than the highest level determined in the blood during the same day as shown in table 6.

In table 7 are listed the toxic reactions that occurred in this series. Under encephalopathy are listed four cases in which delirium, irrationality, or convulsions developed after administration of the drug. There were seven other cases in which encephalopathy was present before treatment was instituted. One case of hemoglobinuria is listed as hematuria. Nitrogen

retention was shown by elevation of the non-protein nitrogen. In the four cases, the highest determination for each was 46, 100, 120 and 120 mg per cent. We were not concerned with cyanosis due to the drug.

COMPLICATIONS

Three patients developed empyema after treatment was started. One of these patients (number 52) died. One of the two survivors required thoracotomy. A pleural effusion developed in six other cases (11.1 per cent), including one fatal case. There were no cases of meningitis, endocarditis, otitis or phlebitis in this group of patients.

Taplin, Jacox and Howland⁶ have reported the use of sodium sulfapyridine by hypodermoclysis in from 0.3 to 0.7 per cent solution in physiologic solution of sodium chloride without the observation of a single local reaction in any of the more than 50 patients treated by this route. In our series, however, we encountered, in 11 cases, antecubital thrombosis with surrounding soreness and induration associated with the intravenous infusion of 0.27 to 0.53 per cent solution of sodium sulfapyridine.

MORTALITY

In an unselected series of 54 cases of lobar pneumonia, not much importance may be attached to the mortality rate. However, since our rate of 14.8 per cent is higher than that reported as occurring in many series of lobar pneumonia treated with sulfapyridine we would like to summarize our fatal cases.

Case 47. A 52-year-old male had been a deaf and dumb moron since he had had meningitis at the age of three years. He was admitted with Type XX left lower lobar pneumonia of unknown duration. After two infusions of 4.8 grams of sodium sulfapyridine, he developed violent tonic and clonic convulsions. The temperature, pulse, and respirations were normal after the third infusion, but the convulsions continued with such severity that on the third day the drug was stopped after seven injections. The next day the temperature rose to 103.2 degrees. Type XX anti-serum, 100,000 units, was given. On the fifth day his clinical condition was so much worse that the drug was resumed. Five infusions of 4.5 grams were given. On the sixth day convulsions and pulmonary edema were terminal events.

Case 48. A 49-year-old male was admitted with Type XIV right lower lobar pneumonia of two days' duration. Temperature on admission was 106.0 degrees. Subsequently, the temperature varied between 101.4 and 107.0 degrees. The initial leukocyte count was 4,600. This gradually increased to 13,550 on the fifth day. During the second hospital day the patient became irrational. During the third day 300,000 units of Type XIV anti-serum were given. An effusion was present. Anuria developed during the fourth day and persisted until the patient died during the fifth day of hospitalization.

Case 49. A 64-year-old female was admitted four days after the onset of left lower lobar pneumonia of undetermined type. During the first six hospital days the temperature varied between 98.6 and 102.4 degrees. On the seventh day the temperature rose to 105.6 degrees. Peripheral circulatory failure developed and persisted until the patient died during the ninth hospital day. When failure developed,

the administration of the drug was changed from intravenous infusions to rectal instillations without benefit.

Case 50. A 55-year-old male was admitted with Type I right lower lobar pneumonia of three days' duration. He was irrational on admission. The blood culture was positive for Type I pneumococci. Thoracentesis on the second day yielded 300 c.c. of pus containing the same organism. During the second and third days 300,000 units of Type I anti-serum were given. Hematuria developed during the third day shortly before the patient died 76 hours after admission.

Case 51. A 73-year-old male was admitted with Type III right upper and middle lobar pneumonia of unknown duration. This patient had attended the out-patient clinic since 1932 with angina pectoris. In 1937, he was admitted for treatment of coronary artery disease. Generalized arteriosclerosis was pronounced. On the second hospital day the blood non-protein nitrogen was 120 mg. per cent. During the same day peripheral circulatory failure developed and persisted until the patient died on the third day.

Case 52. A 59-year-old male was admitted three days after the onset of Type III left upper and lower lobar pneumonia with effusion. On the second hospital day a maculopapular rash developed over the abdomen, shoulders, wrists and knees after two infusions of sodium sulfapyridine had been given. The drug was stopped, but the rash increased. During the same day 200,000 units of Type III anti-serum were given. During the fifth day a thoracentesis yielded 350 c.c. of cloudy fluid containing Type III pneumococci. Because of the seriousness of the patient's condition, sodium sulfapyridine infusions were resumed and 100,000 additional units of anti-serum were given, but the patient died during the sixth hospital day.

Case 53. An 84-year-old male was readmitted after being at home for 10 days following hospitalization of a month for senility and emaciation. A roentgenogram revealed left lower lobar pneumonia, but the clinical findings were not compatible with lobar pneumonia until the fourth day when the temperature rose to 103.2 degrees. Sodium sulfapyridine was begun then but the patient died the next day. Autopsy revealed: left lower lobar pneumonia, pulmonary tuberculosis with a cavity four centimeters in diameter in the right upper lobe, bilateral fibrous pleurisy, generalized arteriosclerosis with calcification of the larger vessels, concentric myocardial hypertrophy, granular contracted kidneys, chronic cholecystitis with cholelithiasis and hydrops of the gall-bladder, emaciation and decubitus ulcers.

Case 54. A 76-year-old female, senile and emaciated, was admitted with right middle and lower lobar pneumonia of four days' duration. On admission her temperature was 99.6 degrees. It did not rise above 100.6 degrees. Before the sixth infusion of sodium sulfapyridine the blood level of free sulfapyridine was 25 mg. per cent. This infusion of 2.0 grams in 750 c.c. of 5 per cent dextrose in physiological saline was given in one hour. The patient died 10 minutes after the completion of the infusion and 32 hours after admission.

CONCLUSIONS

1. The intravenous administration of a solution of sodium sulfapyridine monohydrate is a safe procedure.
2. Sodium sulfapyridine should be used intravenously only when there is a special indication.
3. The concentration of free sulfapyridine in the blood after intravenous administration is usually higher than after oral ingestion but:
 - (a) Unusually high concentrations seem no more effective than those of 3 to 4 mg. per cent.

- (b) There is no added constancy of the blood level of free sulfapyridine after intravenous administration.
- (c) The mortality rate of 14.8 per cent after the routine administration of sodium sulfapyridine intravenously is not lower than the reported mortality rate after oral administration of sulfapyridine.
- (d) Complications of lobar pneumonia are not prevented by the intravenous injection of sodium sulfapyridine.
- (e) Toxic reactions in this series are of about the same or of slightly greater frequency than in reported groups receiving the drug orally.

REFERENCES

1. MARSHALL, E. K., JR., and LONG, P. H.: The intravenous use of sodium sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 1671.
2. FINLAND, M., LOWELL, F. C., SPRING, W. C., and TAYLOR, F. H. L.: Parenteral sulfapyridine; the intravenous use of sodium sulfapyridine and a report of clinical and laboratory observations on the use of a glucose-sulfapyridine solution, *ANN. INT. MED.*, 1940, xiii, 1105.
3. ABERNETHY, T. J., DOWLING, H. F., and HARTMAN, C. R.: The treatment of lobar pneumonia with sulfapyridine and sodium sulfapyridine, with observations upon effective blood levels, *ANN. INT. MED.*, 1940, xiii, 1121.
4. FLIPPIN, H. F., LOCKWOOD, J. S., PEPPER, D. S., and SCHWARTZ, L.: The treatment of pneumococcic pneumonia with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 529.
5. PLUMMER, N., and ENSWORTH, H. K.: Sulfapyridine in the treatment of pneumonia, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1847.
6. TAPLIN, G. V., JACOX, R. F., and HOWLAND, J. W.: The use of sodium sulfapyridine by hypodermoclysis, *Jr. Am. Med. Assoc.*, 1940, cxiv, 1733.

PHONOCARDIOGRAPHY AND ITS CLINICAL CORRELATION *

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EVER since the discovery of the heart sounds by Harvey in 1626, there must have been a desire for their graphic representation on the printed page. For, according to Orías and Braun-Menéndez¹ the skeptics of that day denied the existence of the heart sounds even after Harvey's classical description of the same. The refusal to recognize Harvey's discovery went so far as for one authority to state that such perfect auditory acuity as to hear heart sounds could exist only in London and nowhere else in the world. Visual demonstration would certainly have helped then to convince doubters of facts, as it frequently does even now.

The necessity for graphic recording of heart sounds must have arisen again almost two centuries later when Laennec defined and interpreted heart murmurs. It must have been urgent again to invoke the visual sense as an aid to the auditory sense, in order to locate the precise position of the murmur in the heart cycle. And, even today, the necessity for such help from the visual sense organ is still apparent.

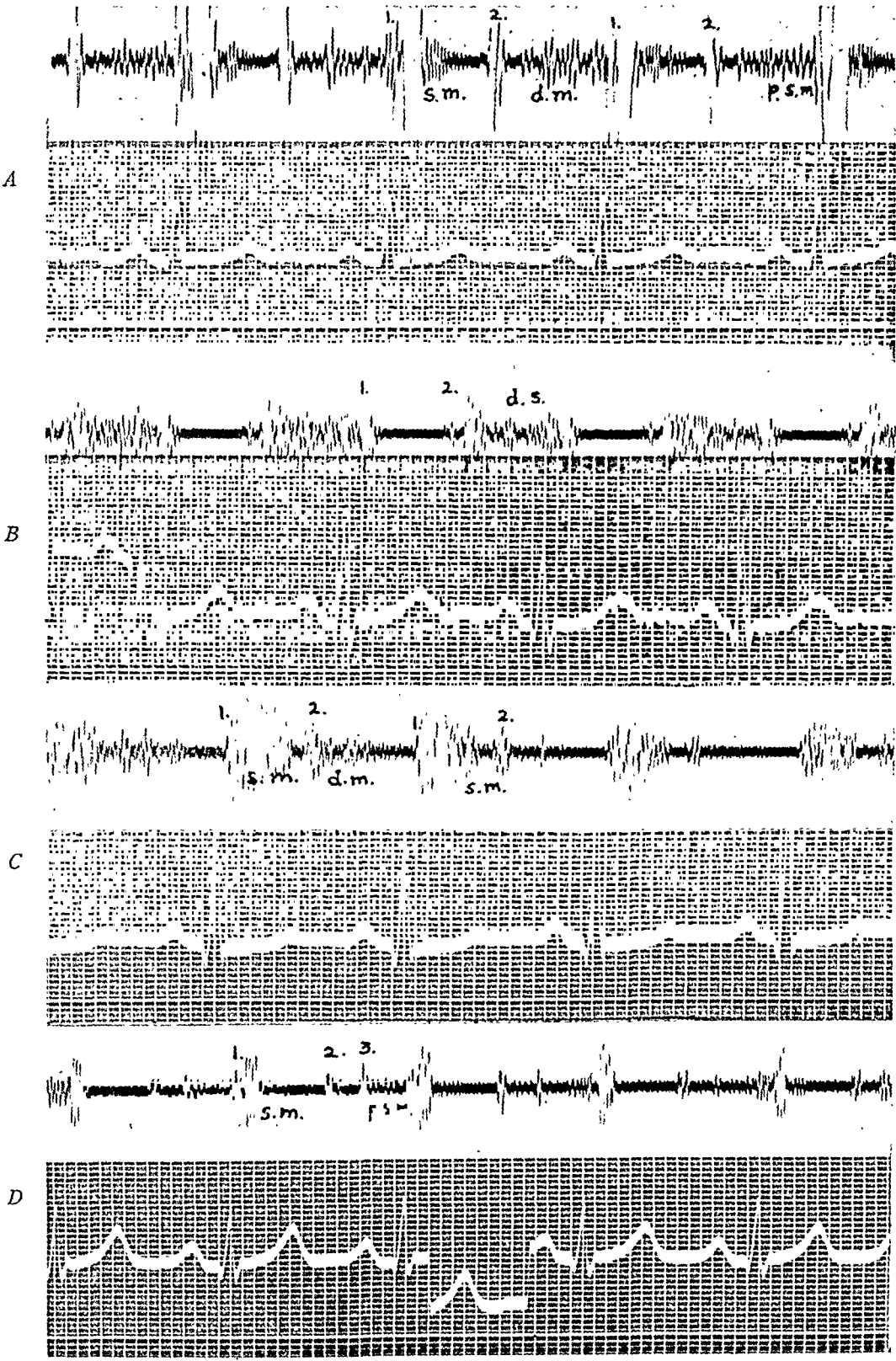
Since then many attempts at graphic representation of the heart sounds and heart murmurs have been made. But it was not until the close of the 19th century that real progress had been made and that was with the introduction of Einthoven's method of electrophonic amplification and recording.² Subsequently various devices have been introduced, the most popular ones being the electrical or indirect method and the capsular³ or direct method of recording heart sounds and murmurs.

The normal heart sounds as well as the various murmurs have already been studied and recorded by many investigators and have been clearly defined as to duration of each sound, number of vibrations for each sound and murmur.^{1, 4, 5, 6} This paper deals with the clinical correlation of phonocardiography and organic heart disease.

PROCEDURE

Two hundred cases of the most common varieties of organic heart disease were studied graphically and clinically. The heart sounds were recorded simultaneously with the electrocardiogram on the Cambridge electrocardio-stethograph.⁷ The number of patients included 190 adults and 10 children. The adults varied in age from 18 to 76 and included only 14 females. The 200 patients included 181 definitely diagnosed cases of or-

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From the U. S. Public Health Service.



ganic heart disease in various stages of functional capacity; 9 were unclassified and 10 were considered possible or potential heart disease.

In order to evaluate the efficiency of the recording instrument as compared with the clinical findings, all heart sounds, murmurs, and gallop sounds were recorded separately, after each examination. The graphic record of the patient, made soon after the examination and with the individual in the same position, was interpreted independently and recorded in parallel column on the patient's chart. The criteria of Wiggers,⁴ Boyer, Eckstein and Wiggers⁵ and of Orías and Braun-Menéndez,¹ were used for determining what constitutes a normal heart sound and what constitutes a murmur. Thus the first sound recorded from the apex consists of 5 to 11 vibrations and extends over a period of 0.06 to 0.11 second. The second sound consists of 3 to 4 vibrations and extends over a period of 0.04 to 0.06 second. The third sound consists of 1 to 3 vibrations and takes place 0.11 to 0.14

TABLE I
Two Hundred Patients Studied
Diagnosis

	Rheu- matic	Hyper- tensive	Syphi- litic	Coro- nary	Congen- ital	Undeter- mined	Potential and Possible	Total
No. of Patients	70	44	35	26	6	9	10	200

second after the beginning of the second sound. And the fourth or auricular sound begins 0.04 second after the origin of the P-wave in the electrocardiogram and consists of 2 to 5 vibrations. The cycles denoting the murmurs following the normal sound or replacing the sound are usually indistinguishable from the vibrations of the normal sound. It is the number of vibrations and the time factor above the maximum number of cycles encountered in normal sounds that determine the murmur. Systolic murmurs including the sound may have 13 to 35 vibrations or even more and may extend over a time period to reach or pass the second sound: or, it may be so short as to extend over a period not longer than 0.02 to 0.03 second past the first sound.

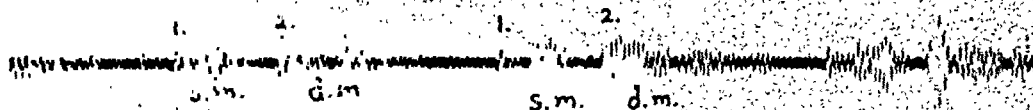
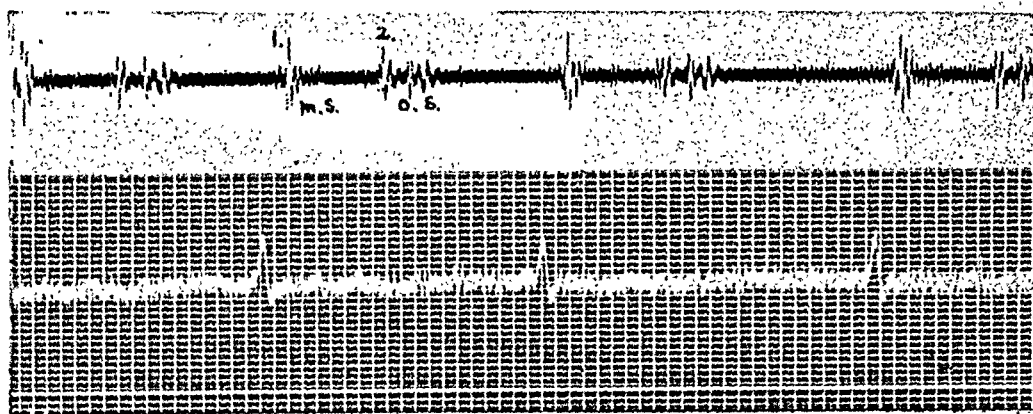
The diastolic murmur together with the second sound consist of 7 to 45 vibrations. It may be so short as to extend over a period of 0.07 second, or over the entire diastole and even continue with a late diastolic or presystolic murmur to merge with the succeeding first sound.

FIG. 1. *A.* Rheumatic heart disease, mitral stenosis and insufficiency with late diastolic or presystolic murmur. *B.* Rheumatic heart, mitral stenosis and insufficiency with aortic insufficiency. *C.* Rheumatic aortic insufficiency and stenosis, with mitral insufficiency. *D.* Rheumatic heart disease with physiological third sound.

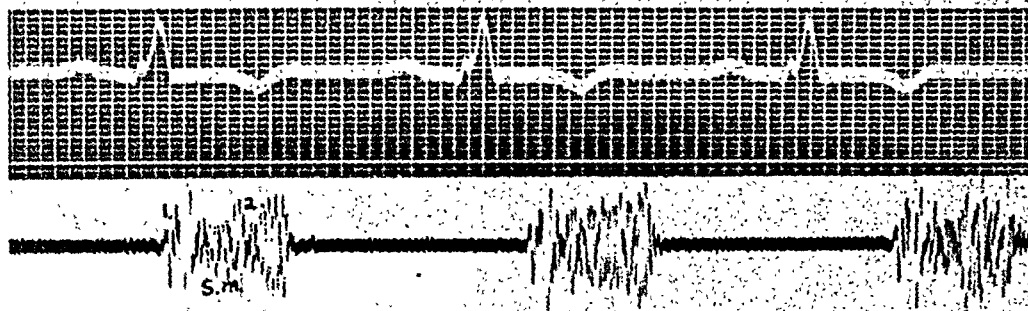
S.M.—Systolic murmur

D.M.—Diastolic murmur

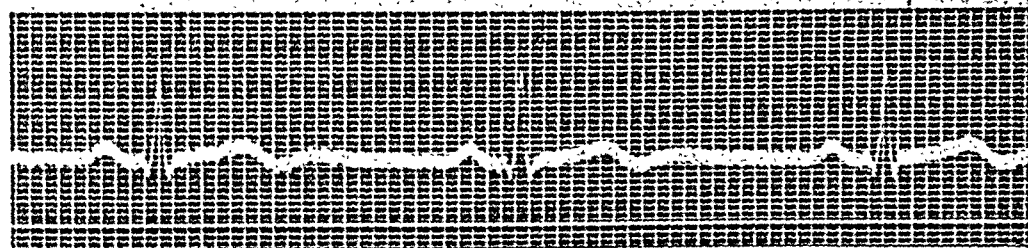
P.S.M.—Presystolic murmur.



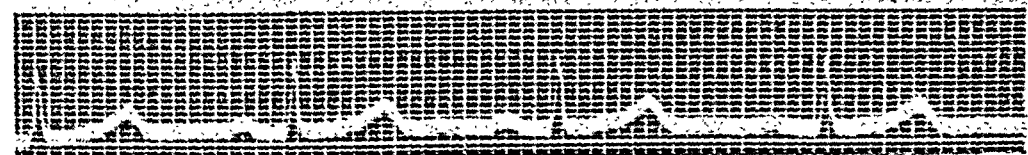
B



C



D



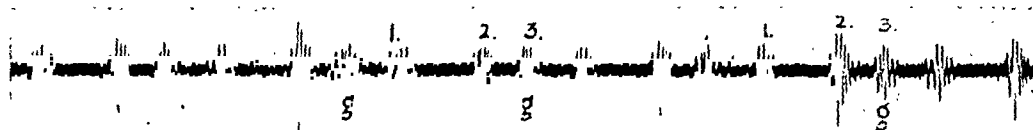
Based on the above criteria there was a remarkable uniformity and agreement between the clinical description of the murmurs and the graphic interpretation of the same. However, in about 10 per cent of the diastolic murmurs of aortic insufficiency the interpreted graphic record did not correspond with the clinical record. That is, the murmur was definitely heard on physical examination and through the stethophone but was not represented by vibrations on the phonocardiogram. If the amplification was increased, many adventitious vibrations appeared and distorted the base line or silent period between sounds. On the other hand, late diastolic murmurs or pre-systolic murmurs of mitral stenosis were occasionally recorded graphically but were not described clinically, only to be confirmed on subsequent re-examinations. Systolic murmurs were almost always recorded graphically when they were described clinically. At no time, however, was a systolic murmur recorded graphically when it was not heard on physical examination but it was not recorded in eight instances where it was repeatedly heard on examination. It was, however, only in the distantly heard murmurs of low intensity that the instrument failed to record them or did so poorly.

Thus out of 168 clinically recorded systolic murmurs among the 200 patients studied, 160 were recorded graphically. Out of the 75 clinically recorded diastolic murmurs, only 67 were recorded graphically. But late diastolic murmurs were recorded graphically in five instances more than it was described clinically.

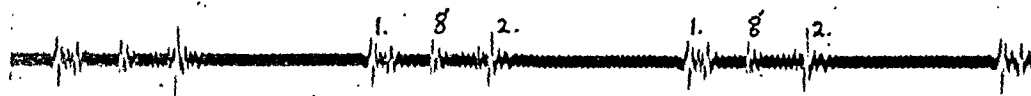
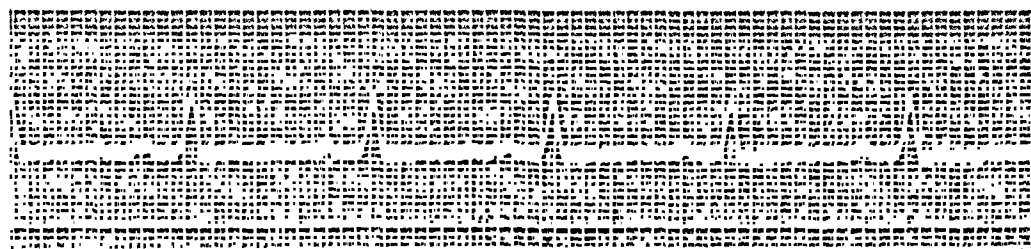
THE THIRD AND FOURTH SOUNDS

It is in the phase of the cardiac cycle when extra sounds are frequently encountered that the recording instruments serve mostly. Both the third as well as the fourth sounds are often missed on physical examination, and when either one of these is described clinically it is not always placed in its exact position in the cardiac cycle. Such differentiation, that is whether the additional sound heard on examination is a third sound following the second, or is a fourth or auricular sound may not be of much clinical significance but it indicates the advantage of graphic recording over the ear, for on the phonocardiogram it is at once definitely recorded and in its exact sequence. Moreover, in cases of doubt with reference to clinical gallop it is important to definitely and precisely locate the extra sound; whether it is in mid-systole which is interpreted as systolic gallop or mid-systolic click⁸; whether it occurs soon after the second sound and, therefore, falls in the category of the opening snap of mitral stenosis, or whether it is a third sound, protodiastolic gallop, or an accentuated auricular sound, or pre-systolic gallop.

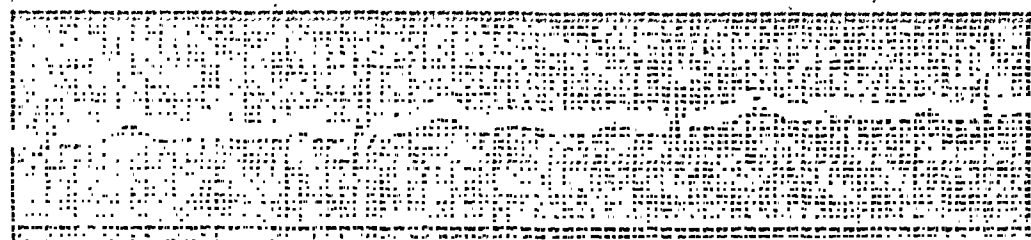
FIG. 2. *A.* Rheumatic heart disease with auricular fibrillation and opening snap of mitral stenosis. Vibrations of murmurs barely visible because of diminished amplification to visualize the third sound (O.S.—opening snap). *B.* Syphilitic aortic insufficiency with aneurysm. *C.* Sclerotic aorta with aneurysm. *D.* Congenital patent ductus.



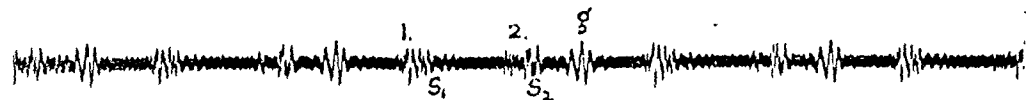
A



B



C



D



Extra sounds were recognized clinically in 48 instances. They were described as a third sound in 42 patients and as a fourth sound in six patients. But they were graphically recorded 21 times as a fourth sound and 37 times as a third sound, indicating gross errors in timing and locating the extra sound with reference to its exact position in the cardiac cycle and also failure in recognizing it altogether in over 15 per cent of the individuals in whom extra sounds were present.

Of the 37 graphically recorded third heart sounds, 17 were described clinically as the opening snap in mitral stenosis, 11 as protodiastolic gallop and nine were classed as physiological third heart sounds. Of the 21 graphically recorded fourth heart sound, ten were clinically considered presystolic gallop, three as presystolic and protodiastolic gallop coexisting, and

TABLE II

Comparative Graphic and Clinical Record of Murmurs, Third and Fourth Heart Sounds

Organic Heart Disease	No. of Cases	Murmurs				Third Sound		Fourth Sound	
		Graphic		Clinical		Graphic	Clinical	Graphic	Clinical
		Sys-tolic	Dias-tolic	Sys-tolic	Dias-tolic				
Rheumatic	70	66	52	68	50	15	14	7	3
Hypertensive	44	26	—	27	1	9	13	8	3
Syphilitic	35	24	20	27	23	4	3	—	—
Coronary	26	23	—	23	1	4	6	3	—
Congenital	6	6	—	6	—	—	3	2	—
Possible and Potential	10	8	—	8	—	2	3	2	—
Undetermined	9	9	—	9	—	3	3	3	—
TOTAL	200	162	72	168	75	37	42	21	6

eight were considered auricular sounds in cases of flutter, congenital heart disease, nodal rhythm, A. V. block, and in two patients of active rheumatic carditis, and in two others classified as possible or potential heart disease, one of whom had a thoracoplasty in the cardiac area, allowing the auricular sound to be distinctly audible.

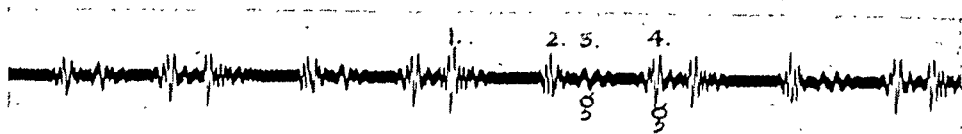
GALLOP RHYTHM

Gallop rhythm exclusive of systolic gallop is a clinical entity and implies established or impending heart failure.^{8, 9} Graphically gallop rhythm is indistinguishable from the physiological third sound or from the fourth auricular sound.

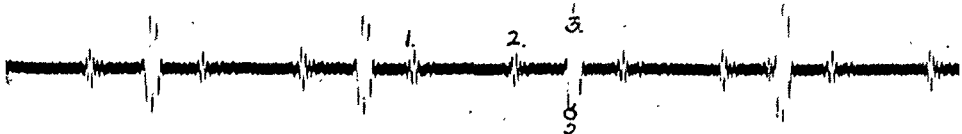
Three different types of gallop rhythm are now recognized⁸: presystolic,

FIG. 3. A. Hypertensive heart disease with presystolic gallop. B. Systolic gallop in a case of possible organic heart disease. C. Protodiastolic gallop in active rheumatic carditis. D. Summation gallop with split first and second sounds in left bundle branch block.

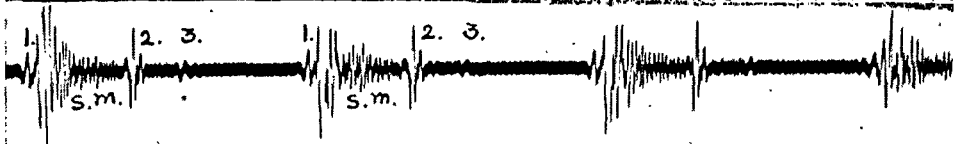
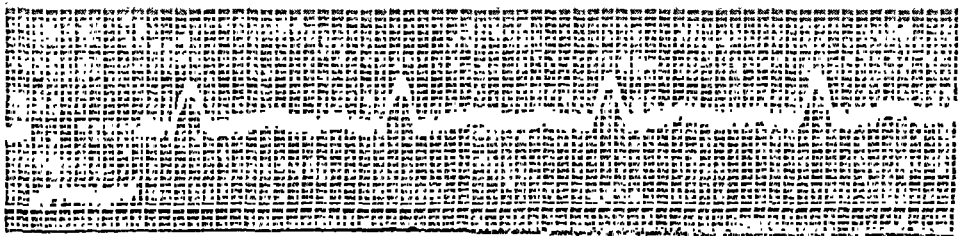
S₁—split first sound. S₂—split second sound.



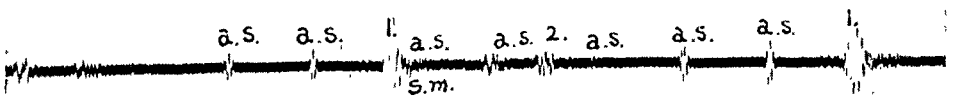
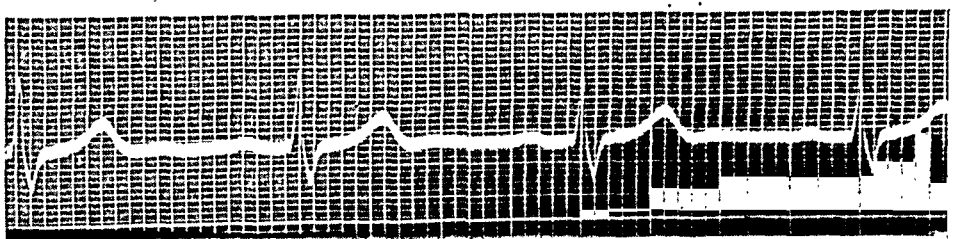
A



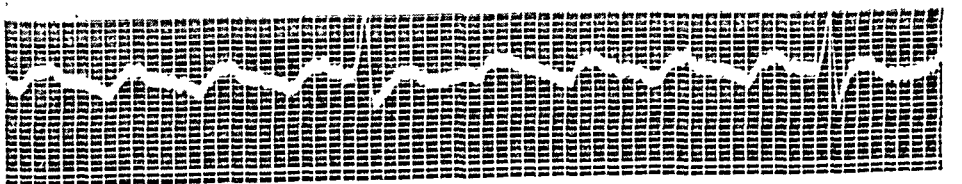
B



C



D



protodiastolic and summation gallop. Both former types may coexist distinctly in one patient, and when the heart rate rises the two extra sounds meet to form summation gallop. The importance of systolic gallop or mid-systolic click is still open to question. Clinical gallop rhythm must be distinguished from the occasional loud, presystolic or auricular sound heard frequently in the young, from the physiological third sound and from the opening snap in mitral stenosis. Rarely it can also be confused with a reduplicated second sound. Graphically the protodiastolic sound is distinguished from the opening snap in mitral stenosis in that the latter falls between 0.08 and 0.11 second after the second sound and is fairly constant in its location in the cardiac cycle, while the third and protodiastolic sound occurs 0.11 to 0.14 second after the second sound.

Among the 200 patients studied, clinical gallop rhythm was recorded in 26 patients. It was noted clinically and recorded graphically in 11 individuals among the 44 studied in the hypertensive group. It was described in five patients among the 70 in the rheumatic group; in five others among the 35 studied in the syphilitic group, and in five out of 26 in the coronary disease group. Whenever clinical gallop was noted it was almost invariably also recorded graphically. In three additional cases it was recorded graphically and was missed clinically in patients of established cardiac failure.

Of the 26 graphically confirmed clinical gallop, 40 per cent were protodiastolic in time, 40 per cent presystolic in time and 20 per cent were mixed and summation gallop. In only about half the number with gallop rhythm was there agreement between the clinical and the graphic record as regards timing.

Systolic gallop rhythm was recorded graphically three times but noted clinically only once. It occurred once in left bundle branch block in syphilitic aortic insufficiency and twice in patients among the potential or possible heart disease group.

SUMMARY AND DISCUSSION

The graphic recordings of heart sounds and heart murmurs of 200 patients of organic heart disease were studied simultaneously and independently of their clinical records.

Based on established criteria which divide the normal sound from the ensuing murmur by the number of vibrations and time relation, and from a careful correlation with the clinical records of the individuals studied, it is concluded that graphic recording of sounds and murmurs cannot replace the trained ear. Indeed in many instances the ear is more trustworthy than

FIG. 4. *A.* Presystolic and protodiastolic gallop in acute myocardial infarction. *B.* Presystolic gallop in intraventricular block with hypertension. *C.* Third heart sound and systolic murmur of mitral insufficiency of undetermined etiology. *D.* Auricular flutter in rheumatic heart disease with auricular sounds.

A.S.—Auricular sound. G—gallop.

the recording instrument. This is particularly true in short systolic murmurs of low intensity, and even more so in cases of soft, blowing diastolic murmurs of aortic insufficiency. The phonocardiograph cannot be relied upon for distinguishing functional from organic murmurs, any more than the ear alone can be relied upon. It is, however, in the third and fourth phases of the cardiac cycle that the recording instrument becomes of great value, since in a tachycardia it is frequently difficult, clinically, to place an extra heart sound in its exact position in the cardiac cycle, and often the extra sound is missed altogether, particularly when murmurs coexist. The fourth sound in such hearts is either not heard at all clinically or when heard is rarely placed in its precise position in the heart cycle. It is really in this phase of cardiac activity where extra sounds appear that graphic recording has greatly contributed. Phonocardiography is also of inestimable value in training the ear to greater acuity with reference to cardiac auscultation and as such should be of aid in teaching. Lastly, in being able to provide a record for future study at leisure and for comparison with subsequent tracings, the phonocardiogram serves the same purpose in relation to auscultation as a roentgenogram which supplements fluoroscopy.

REFERENCES

1. ORÍAS, O., and BRAUN-MENÉNDEZ, E.: The heart sounds in normal and pathological conditions, 1939, Oxford University Press, London.
2. EINTHOVEN, W.: Die Registrierung der Menschlichen Herztöne mittels des Saitengalvanometers, *Pflüger's Arch.*, 1907, cxvii, 461.
3. FRANK, O.: Die Theorie der Segmentkolbenkapsel, *Ztschr. f. Biol.*, 1913, lix, 526-530.
4. WIGGERS, CARL J.: *Physiology in health and disease*, Third Edition, 1939, Lea and Febiger, Philadelphia.
5. BOYER, NORMAN H., ECKSTEIN, RICHARD W., and WIGGERS, CARL J.: Characteristics of normal heart sounds recorded by direct methods, *Am. Heart Jr.*, 1940, xix, 257-274.
6. MCKEE, M. H.: Heart sounds in normal children, *Am. Heart Jr.*, 1938, xvi, 79-87.
7. LOCKHART, M. L.: Stethograph, *Am. Heart Jr.*, 1938, xvi, 72-78.
8. WOLFERTH, CHARLES C., and MARGOLIES, ALEXANDER: Gallop rhythm and physiological third heart sound; characteristics of sounds, classification, comparative incidence of various types and differential diagnosis, *Am. Heart Jr.*, 1933, viii, 441-461.
9. O'FARRELL, P. T.: What is gallop rhythm? *Irish Jr. Med. Sci.*, 1939, xxxiii, 729-739.

PROBLEMS OF ACUTE INFECTIONS *

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It is my pleasure today to speak to you concerning some of the problems which have to do with the everyday care of the patient sick with one or another of the acute contagious diseases. In this presentation I will not attempt to review the recent literature on the subject and will not endeavor to give you the last word in the experimental problems nor the laboratory studies of these diseases; I will simply attempt to give you a few of the diagnostic procedures which I have found of value and to discuss succinctly some of the methods of treatment I have employed in the contagious disease services at the Charity Hospital. I might add, furthermore, that I have drawn not only upon the cases that have occurred on my services, but also upon those that were on the services of my confrères, Dr. Tripoli and Dr. Stulb, in charge of the other two contagious disease services.

SCARLET FEVER

Scarlet fever is one of the common diseases which usually are diagnosed without any degree of difficulty. However, in the milder cases the diagnosis is often extremely hard. Needless to state it is of importance to make the diagnosis because of quarantine-public health regulations. Scarlatina sine angina may be fairly common but I am always dubious indeed about the diagnosis of this form of scarlatina sine eruptione. Streptococcal invasion of the nasopharynx is quite usual in childhood. Whether these organisms are ordinary hemolytic streptococcus or whether they are the beta hemolytic streptococcus of scarlatina, it would seem to me a distinction without a very great deal of difference. The throat clears up in a short time with the use of sulfanilamide. I do not think there is any great likelihood of the child disseminating organisms and starting an epidemic if he is kept under partial quarantine for a few days. As a matter of fact, I think that the present regulations for the quarantine of scarlet fever are ridiculous. It does not take four to six weeks for a young patient to recover from the disease. Some years ago we were using antiserum and following its administration, to all intents and purposes, the child would be well in 24 to 48 hours. At the end of the week the throat would show absolutely nothing and we would discharge him. I have never heard of a single child we discharged conveying the organisms to another child but when the health

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authorities learned of this procedure they promptly made us discontinue, although they did reduce quarantine from six to four weeks.

In the diagnosis of the erythema the Schultz-Charlton reaction is of great value, but unfortunately it does not show up clearly in the dark skinned individuals, particularly of course the negro. The eruption of scarlet fever is characterized by formation of innumerable small papules. These papules can be observed readily by the simple procedure of taking a small pocket flashlight, holding it at almost right angles to the skin and close to it so the shadows of papules are cast on the skin. These papules then can be observed clearly and distinctly.

In regard to the use of serum, there is no question but that it is one of the most efficacious of the antisera. If a child is brought into the hospital in the afternoon and given the serum, the next day the rash will be gone, the temperature will be normal and the angina well on its way to a normal appearing throat. We have, as have many physicians in the past few years, discarded the use of serum except in the exceptional case, because this particular disease at this period seems to be on the downgrade in so far as severity is concerned. The disease runs a mild course; complications are few and far between. As a matter of fact we had not seen any severe septic cases for nearly five years, until last spring when we had three patients who were extremely ill, had marked adenopathy with pus formation and long continued fever. Because of the relative mildness of the disease and the prompt recovery of the patients, we, as many of the doctors with whom I have talked, felt that the almost invariable serum reaction which occurred after its use was more trouble-making and caused more disturbances than did the disease unmodified by serum. As has every one else, we have been using of late sulfanilamide in the treatment of these patients, as in all other infectious diseases. The results apparently are remarkable but it is hard to evaluate, as I said, because the disease is such a mild one nowadays the patient is going to get well promptly under any circumstance. To quote from the literature, Thenebe et al.¹ had more than 350 cases of scarlet fever treated with sulfanilamide and neoprontosil. Complications occurred in 9.7 per cent of their patients. Three-fourths of these were allergic or toxic. There is reduction in septic sequelae from 22.2 to 2.18 per cent. They recommend and we concur in this, the use of scarlet fever antitoxin when the sulfanilamide does not give satisfactory results which is only occasionally. They also advise that sulfanilamide be continued for seven or eight days in order to obviate septic complications. In an earlier paper by Wesselhoeft and Smith,² the contrary opinion is expressed. These authors do not think there is a reduction in the incidence of complications, nor is there very much effect on the toxicity, eruption and duration of fever.

In the study of the effect of sulfanilamide on the blood in scarlet fever, French³ found that there was a constant slight depression of the total white count as a result of a diminution in the polymorphonuclears. She cautions

against the administration of sulfanilamide in a patient with a grave infection. Personally I would have no hesitancy in using sulfanilamide, watching the blood count closely and combining it with the antitoxin. Incidentally, I might comment on the diminishing likelihood of the antitoxin causing serum reaction. It is much more highly concentrated than it used to be, consequently these annoying reactions are diminishing.

TULAREMIA

I will speak of tularemia rather briefly because we observed a certain number of these cases in our contagious disease ward. We are fortunate that our cases are almost invariably of the glandular type. They come in with the initial lesion on the thumb or index finger, the adenopathy is pronounced and there is very little difficulty in making the diagnosis. Once in a while we have a typhoid type which is diagnosed entirely as a result of agglutination reactions. We also tried sulfanilamide in the treatment of a few patients. We have not had the results that Curtis⁴ had, who claims the first report of the treatment of tularemia with his new drug. He had, in his patients with severe tularemia, a subsidence of the symptoms two days after administering sulfanilamide.

In the management of these patients there is one precaution which we are insistent upon, namely that the broken-down lymph glands be untouched. If the resulting abscess has to be opened this is not done until it is almost ready to break through the skin.

I place a great deal of reliance upon the blood agglutination reaction. We have had no experience with the antigen skin test as reported by Friedewald and Hunt.⁵ This test is positive in the first week of the disease but nearly all of our patients with tularemia come into the hospital after they have been sick for a few days or longer.

We see many cases of meningitis but we have yet to see one of tularemic meningitis which was recently described by Kimmelstiel and Caldwell.⁶

DIPHTHERIA

The incidence of diphtheria at the Charity Hospital, as elsewhere throughout the country, is diminishing, thanks to the almost universal Schick testing and use of toxoid. Some five years ago we undertook to immunize all children of school age in New Orleans. The campaign resulted in the immunization of some 40,000 children. This was then taken up by the Board of Health and the school authorities now insist a child must be immunized before going to school. The results of our campaign are shown by the following figures: In 1937, 150 children were discharged from the Charity Hospital with the diagnosis of diphtheria, 127 in 1938, 96 in 1939. Practically all of our cases now are children of pre-school age. It is definitely the duty of the family practitioner to immunize a child in early

infancy; certainly by the time the child is two years of age immunity should be conferred by the use of toxoid. What has been accomplished in some of the cities in the North, such as New Bedford, Providence, Rochester, Syracuse, Albany, Grand Rapids and Duluth, in controlling diphtheria is beautifully exemplified in the statistics published yearly by the Journal of the American Medical Association. Further illustrative of this is the experience recorded by Bundeson, Fishbein and White,⁷ who found in 1917, for example, that there occurred slightly over 10,000 cases of diphtheria in Chicago, with a total number of deaths of 1,229 and a death rate per 100,000 of 47.8, whereas in 1937 there were 655 cases with 84 deaths and a rate of 2.3. These physicians recommend three doses of toxoid at monthly intervals. If it could be made a health law that all children must be immunized before two years of age, diphtheria would be almost a non-existent disease. Recently it has been suggested⁸ that children be immunized not only with diphtheria toxoid but also with a combination of alum precipitated tetanus toxoid. This seems like an excellent suggestion.

In the Charity Hospital cases we are interested chiefly in those with laryngeal diphtheria and those children who have cardiac complications. The ordinary types of diphtheria yield promptly and immediately to diphtheria antitoxin with an average dose of 10,000 units. On the other hand, our laryngeal cases are children who die, sometimes from obstruction but more frequently from the complicating bronchopneumonia. They are usually all small children. In spite of enormous doses of antitoxin given intravenously or intraperitoneally and intramuscularly, usually dividing 80,000 to 100,000 units into two doses, one given intramuscularly, the other one or another of the other ways, the children die. At autopsy sometimes the diphtheria exudate will be found to extend down the trachea; sometimes casts of the trachea and the large bronchi may be lifted out bodily. Our results in this type of diphtheria are most distressing.

Cardiac complications are really most interesting. It is a moot question whether or not cardiac complications of diphtheria permanently injure the heart. Personally I do not think that in after-life the diphtheritic myocarditis of childhood will occasion heart disease in an adult. However, this question is of academic rather than of practical importance because the thing to be treated is the sudden acute heart failure which is often associated with vasomotor collapse which may cause sudden death in a child apparently convalescing satisfactorily and well on the road to recovery. Because we had several deaths in children who, although not supposed to be up and about, had gotten out of their beds and then died suddenly, we are very insistent upon a prolonged convalescence after diphtheria. I think this cannot be stressed too forcibly. If a child has a slight tonsillar lesion and is given antitoxin, the exudate disappears in two or three days, the cultures are negative in a week and the child has not appeared particularly sick; it is difficult to insist that such a child should be kept quiet for three weeks and

no active exercise permitted for four weeks. For a period of time we attempted to control the length of convalescence by electrocardiograms but this proved to be impractical because of the size of the service. Now we caution the mother, if the child is discharged, not to let him go about and play and enter into the usual childhood activities of a well child. Certainly this is a precaution which every physician will insist upon did he see occur in his practice the sudden death of an apparently satisfactorily convalescing child.

In the treatment of cardiac failure we lay a good deal of stress on the administration of glucose, depending on it rather than upon digitalis which may be actually contraindicated in certain types of heart failure, or upon caffeine and similar drugs.

MEASLES

During the winter of 1927-28 there was an extremely severe epidemic of measles in the City of New Orleans. This epidemic became so severe and so large was the number of cases that for the only time in my knowledge it was possible to admit to the Charity Hospital only the patients with measles who showed complications. Ordinarily one looks upon measles as an extremely mild disease, one which it is advisable for the child to have before school days, so as to get over with it and to be subsequently immune. One who has gone through a severe epidemic of this disease dreads the possibility that this usually endemic disorder may obtain epidemic proportions. At this time on my service alone there occurred 351 cases. These figures can be contrasted with the incidence of measles in the Charity Hospital on all services in the last three years. In 1937 there were 67 cases; in 1938, 98; in 1939, 96. The mortality was practically nil, two children died but they already had some other complicating condition. On the other hand, during the severe epidemic the children were dying from complicating bronchopneumonia, otitis media with its complications, and a few from encephalitis. As a matter of fact, in the cases of children of two years of age or under, bearing in mind that they already had severe tracheobronchitis when admitted to the hospital, it was almost the exception rather than the rule that they would recover.

During this period of time we were able to obtain six consecutive blood cultures which were positive to an organism which fulfilled Tunnickliff's requirements in every way. We felt very definitely at that time that the condition was due to the specific organism. There is a question whether measles is due to a specific organism or is the result of a virus infection. It seems to be the general feeling among medical men at the present that measles is a virus disease. It might well be possible to have obtained the diplococcus of Tunnickliff by blood culture at this time because it was a secondary invader. Certainly in subsequent blood cultures we have not been able to confirm her work. As further evidence that measles is possibly a virus disease is

the fact that encephalitis is by no means an uncommon complication. In 1928 Hauser and I⁹ reported on eight patients with encephalitis who died, reporting on the autopsy findings in two of these cases. In addition to the eight fatal cases, all of which showed the presence of numerous discrete, punctate hemorrhages throughout the brain grossly, with perivascular hemorrhage around many of the small vessels microscopically, we also had a goodly number of patients who recovered. That this complication is not rare in epidemic measles is further substantiated by a communication from Peterman and Fox.¹⁰ They observed an epidemic in 1933 when there were 13 cases of this complication, and in 1938 there was another epidemic of the disease with 14 instances of postmeasles encephalitis. This complication is associated with a fairly definite syndrome which is expressed by the onset of cerebral involvement on or about the fourth day after the rash has come out. There occurs rigidity in the muscles of the neck, stupor and convulsions. There is a leukocytosis, the spinal fluid is under increased pressure and shows an increase in the number of lymphocytes. The mortality rate, according to these observers, is roughly 30 per cent.

The other complications of measles, otitis media and bronchopneumonia are extremely common. On the other hand, noma is very rare in my experience. I have seen only one patient with this disorder.

The treatment of measles has been good nursing care and that is about all. I have not had the opportunity of using sulfanilamide or sulfapyridine in the complicating bronchopneumonia. In view of the horrible experiences during the great war with streptococcic pneumonia following measles which resulted in the death of many thousands of soldiers, it might be advisable to use this drug should an epidemic arise, irrespective of whether or not the young person has any complications. It might possibly forestall streptococcic pneumonia.

My experience with the use of convalescent serum has been extremely limited; as a matter of fact the little information I have about it is largely from hearsay. I have from time to time requests from doctors for blood serum of children convalescent from measles for use in sickly, undernourished children who have been exposed to the disease or who are living in an epidemic. The results have been excellent, again from hearsay, the serum distinctly modifies the severity of the disease and sometimes apparently prevents it. I believe almost equally efficacious, however, is whole blood given in quantities two or three times greater than the amount of immune serum. The whole blood can be gotten from nearly any adult who has had the disease and whose blood need not be compatible because it may be given into the muscles of the buttocks and thigh either defibrinated or else unchanged. There is now on the market a measles antibody preparation known as immune globulin obtained from human placental blood and tissue, placental blood apparently transmitting antibodies in greater number than normal blood. The advantage of the preparation is, of course,

that it is always on hand, whereas convalescent measles patients are not always available and to a small baby giving whole blood would require a greater amount than it might be possible to inject comfortably. In a recent article McKhann¹¹ reports that placental extract had been used in 2740 cases. He was able to protect 1762 (64.3 per cent) patients, modify the course of the disease in 833 (30.4 per cent), while it had no effect in 145 instances (5.3 per cent). From the work of the Massachusetts observers (McKhann, Eley and others) it would seem to be definitely established that this commercial globulin given in doses of 2 c.c. is of immense value in preventing and modifying measles. As I said, I have had no experience with it or with protective doses of serum because the measles patients I see already have their disease fully developed.

Measles frequently happens in the newborn provided the mother has not had the disease. I have seen infants emerging from the birth canal with a rash in the same stages of development as on the mother. There seems to be a popular conception that because immunity to measles is given by the mother to the child for a period of six months to a year, such immunity can exist irrespective of whether or not the mother has had the disease. If she has not had measles the child will not be protected.

Kohn, Fischer and Resch¹² have checked over the value of parenteral whole blood in the treatment of measles after the rash has appeared. They were unable to find any variation as to the severity of measles in the control group of 758 children, as compared with the test group of 76 children.

WHOOPING COUGH

A great deal of interest in immunizing against pertussis has been aroused in recent years, largely by Sauer,¹³ who has prepared a special vaccine which apparently produces a more or less permanent immunity within a period of some three months. I have had no experience with Sauer's vaccine because when I see the children the disease is already fully developed. I have, as with measles, given to some of my doctor friends convalescent serum from patients on the contagious disease service. They have been skeptical after using it, about the value of convalescent serum in preventing or ameliorating whooping cough. Lucas¹⁴ writes that the passive immunity, lasting not more than three weeks, which is conferred by convalescent serum, is a more effective agent than vaccine in the prevention of whooping cough in children already exposed.

The lymphocytosis which occurs in whooping cough is very well known. Sometimes the total count and the number of lymphocytes increase to remarkable figures. Several years ago we had a child who for some three weeks had a total leukocyte count which remained persistently over 125,000, 99 per cent of which cells were lymphocytes. Needless to state such a picture resembles very closely leukemia but this child's count gradually returned to normal in about six weeks.

Here is a method we find quite efficacious in controlling severe paroxysms of coughing. Ten or 20 c.c. equal parts of olive oil and of ether are injected into the rectum. This is an irritating, burning solution so that the cheeks of the child's buttocks must be held together for several minutes lest the material be expelled. It is definitely beneficial and well worth trying in refractive cases.

For a period of nearly a year all of our patients were treated with roentgen-ray. We could not see any improvement in the length of illness, severity of the cough or control of complications.

CHICKENPOX

Measles is often referred to as the most contagious of contagious diseases but as a matter of fact chickenpox is much more contagious. I have seen 149 cases of chickenpox in the last three years. Practically every child gets it sooner or later after maternal immunity has disappeared. As with measles, chickenpox may occur in the newborn baby if the mother is not immune. Witness the case reports of Campbell¹⁵ and Shuman.¹⁶

The only complication or sequel of any moment in varicella is the secondary infected pox on the face of girl babies and small children. So that they may not scratch the facial lesions we have been accustomed to put a tongue-depressor splint at the bend of the elbow so that the arm cannot be flexed. Recently we have used a very simple contraption of a pasteboard cuff about the elbow joint which can be taken off and put on very much more readily than the splint and which will serve the same purpose.

ERYSIPELAS

On the Charity Hospital contagious disease services there have been admitted in the past three years 197 patients suffering from erysipelas. These patients do not present, as a rule, any marked diagnostic problem. Occasionally the patient may have a cellulitis which is non-specific but as a rule the diagnosis is obvious. There are admitted a certain group of patients who have the so-called recurrent erysipelas. I do not believe that these patients should be classified as true cases of erysipelas. The usual story is that in the past they have had erysipelas, usually of the lower extremity and frequently developing from around a leg ulcer. The patient has sudden fever without prodromes, the area of previous involvement becomes a red to dusky red, the overlying skin is indurated and to all intents and purposes acute erysipelas is present in that extremity. However, within 48 hours the temperature will have subsided, there will have been no extension of the lesion and the skin itself becomes soft and pliable. I believe that these flare-ups represent allergic phenomena in skin previously sensitized, as shown by Amoss, which responds to the presence of an antigen, the specific streptococcus, which has gained entrance somewhere into the

body, most likely in the upper respiratory tract. It may be that some other streptococcus other than a specific one may produce the same result. This is an annoying sequel of erysipelas. In one instance an elderly man was readmitted to the hospital nine times in the course of a year. He was finally persuaded to stay home, rest for 48 hours and not worry about his condition, otherwise I believe he would have kept on coming into the contagious disease ward interminably.

On the whole the results that have been obtained on our respective services with specific antitoxin have not been particularly brilliant. This may be because many of our patients do not enter the hospital until after they have been sick for three or four days. Under any circumstance injection of 40,000 units or more of this antitoxin has not had a very appreciable effect on the severity of the disease nor any outstanding effect on its course.

One of the objectives in the management of the patient is to prevent the spread of the infection of the skin. At one time the older physicians awaited the stopping of the infection at natural boundaries. At one time they used tight adhesive strips placed 1 or 2 cm. above the extending inflammation. A very satisfactory method I have found to stop the spread of the lesion has been to inject the specific antitoxin intradermally about 3 or 4 cm. above the elevated reddened skin, bearing in mind that the causative organism is a centimeter or more ahead of the inflammatory reaction. A wheal is produced; at the base of this wheal another wheal is produced; this is repeated until the inflammation is completely circumscribed. By this method it has been possible to limit the extension of the disease process.

The modern treatment of erysipelas is by the use of sulfanilamide. We have treated now some 40 patients with erysipelas with sulfanilamide and have had excellent results. Following a large initial dose we give 1 gram every four hours to the average adult patient, omitting one dose at night. With the sulfanilamide an equal amount of sodium bicarbonate is given. The disease comes to a relatively abrupt cessation in two or three days. Sometimes the results are quite spectacular. We have been maintaining smaller doses of sulfanilamide following the cessation of fever and the extension of the inflammation for three or four days and cutting down approximately to about one-half the dose maintained when the patient was febrile.

ACUTE LYMPHOCYTIC CHORIOMENINGITIS

We have had in our hospital services a series of patients, 12 in number, who suffered from this virus disease which has been considered to be a rather relatively rare condition. This group of cases has been reported by Tripoli and Fader.¹⁷ The virus that is responsible for this condition is capable of being transmitted to monkeys, guinea pigs and other experimental animals by a variety of routes. The disease is transmitted by direct in-

oculation. Toomey¹⁸ reported on 70 patients to whom apparently the virus was transmitted with a considerable degree of contagiousness.

It is rather interesting that this disease, which was first recognized by Wallgreen,¹⁹ has become a rather prevalent disease. Cases have been reported from various parts of the United States as well as from Europe and Australia.

Postmortem findings are almost unknown because people with this condition do not die.

The clinical syndrome is one of relatively mild prodromal symptoms, followed by a quite abrupt onset which suggests very strongly the onset of meningitis, there being nausea and vomiting, high fever, headache, disturbed psyche, and rigidity of the muscles of the neck. Given a patient who is apparently suffering from acute meningitis the lumbar puncture is performed and it is found that the cell count ranges from 250 to 1000. Stiffness of the neck was present in all cases reported by Tripoli and Fader. The spinal fluid was under slightly increased pressure and the differential cell count showed from 50 to 100 per cent of lymphocytes. It has been our experience that very promptly the diagnosis is made of tuberculous meningitis. Then the patients begin to improve. They develop no cerebral or nervous complications. The duration in this series of cases ranged from five days to 16; in only three instances did the disease last longer than 10 days. The only treatment that was employed was drainage of the spinal canal from time to time. This might be said to have been more for the purpose of obtaining spinal fluid for study than for real treatment.

The most satisfactory feature of this condition is the intense relief the doctor feels when, in the course of two or three days, the patient he thought had tuberculous meningitis, proceeds to improve. Instead of going on to death he gets well rather rapidly.

I am rather of the impression this disease is more frequent than can be shown statistically. I believe it is quite possibly present in patients who have fever, headache, drowsiness and show some slight rigidity of the neck. They may be accused of having any one of a number of acute infections, possibly grippe in most instances. They are not extremely ill and so lumbar puncture is not done and without the spinal fluid survey there is no positive evidence to indicate that this condition is present. If spinal fluid examinations were done routinely just as are leukocyte counts, maybe there would be a marked accretion in the number of cases. This would at least be of epidemiologic interest.

PNEUMOCOCCAL MENINGITIS

One cannot but help being enthusiastic about sulfanilamide and sulapyridine. The outstanding and astounding results with the use of these drugs in some of the severe diseases and infections make it impossible to

blame a man for being hyperenthusiastic. I do not know of any disease in which the beneficent effects of the drug are better exemplified than in pneumococcal meningitis. When I had a patient come into the ward with signs of meningitis and when the thick inspissated spinal fluid of pneumococcal meningitis was drawn out through the lumbar puncture needles, my reaction promptly was to say the patient would be dead in a very short time. Within the last six weeks there have been on our contagious disease services six patients with pneumococcal meningitis; four of them have recovered without a single complication. Their recovery has been prompt and dramatic. The drop in temperature has been almost by crisis. Bear in mind that these patients were extremely ill when they came in. A number of them were in coma and unconscious on admission to the hospital. The incident of a small boy, for example, will illustrate what has happened in every case. This child could not be aroused; he was actively delirious. Early the morning after admission the delirium had subsided to a great extent although he still had to be restrained, but by the middle of the morning he could be aroused so he could understand what was going on. The next day the sensorium was entirely clear and from then on he proceeded to get well. Of these six patients, four survived, and two died, both of whom succumbed very promptly on admission to the hospital. One died within four hours after admission, the other patient had been sick for several days before he entered the ward.

Fortunately meningitis in its acute onset is characterized by an obvious and marked symptomatology. The patients are severely ill, they are admitted without delay to the hospital so that they can be treated early and treatment is not put off for several days or longer as it may be with typhoid fever or even with erysipelas. Every one has agreed that the earlier the sulfapyridine is administered the greater is the chance for recovery.

We have not been limiting our treatment entirely to sulfapyridine. We have also used specific serum in every instance except one, but we have used specific serum before and have never had the dramatic and spectacular results that have been obtained with the serum and sulfapyridine combined. It looks very much as if the sulfapyridine was the important factor. The therapeutic regimen has been as follows: The spinal canal is drained and such drainage is repeated every six or eight hours until the spinal fluid is clear or the cell count is markedly diminished and there are no signs of intracranial tension. The patient is given, as soon as the diagnosis is made and the serum typed, the specific antitoxin intravenously. The patient is also given sulfapyridine either by mouth, which in most instances he cannot take, or else the soluble salt intramuscularly.

MENINGOCOCCIC MENINGITIS

The diagnosis of meningitis is fortunately relatively simple. A patient presenting headache, a clouded sensorium, abrupt onset of symptoms and

rigidity of the neck is subjected to spinal puncture. The diagnosis of the specific type of meningitis is made by laboratory methods promptly so that meningococcic meningitis is one of the diseases that are early recognized by the physician. Occasionally a patient is seen in whom the symptoms are not pronounced. I remember very well indeed a young girl who was pregnant and presented a low degree of fever. Every possible type of laboratory examination was made in order to discover the cause of the fever. Finally after a week or ten days some bright diagnostician came along and suggested a spinal puncture which was done and turbid fluid obtained. The patient was transferred to the contagious services at Charity Hospital and proceeded to recovery uneventfully, about three months later giving birth to a healthy child. Lumbar puncture, of course, is the important procedure in making the diagnosis. Stiffness of the neck is the only physical sign early in the course of the disease that is of any moment. Kernig's sign is absolutely worthless except for its negative value.

In the treatment of our meningococcic meningitis patients we have been running the gamut of therapeutic procedures from those suggested by others, to those which we have devised ourselves. Tripoli²⁰ reported several years ago on a considerable series of cases. Serum was used intramuscularly, intravenously, intraspinally, Prengle's iodide was injected in the carotid, continuous drainage through combined cistern and lumbar puncture was employed together, in combination or singly, and always our results have been rather poor. About 50 per cent of our patients have died, a higher incidence than was being obtained at the same time in New York as Josephine Neal brought out in her discussion of Tripoli's paper. Of late we have been using antitoxin intramuscularly and intravenously. I would suggest that the first dose be given intravenously with, of course, the usual precautions appropriate to the giving of any intravenous injection of serum, employing 20-30,000 units diluted to 200 c.c. with normal salt solution. The injection should be given slowly, and simultaneously the same sized dose of serum should be given intramuscularly. This dose is repeated according to the reaction of the patient in 24 hours. It may be diminished as the patient improves. As a rule it is not necessary to give more than 100,000 units intravenously. At the same time sulfanilamide is started. If the patient is delirious and is unable to swallow, sodium sulfanilamide is injected intramuscularly. The initial dose is approximately 4 to 6 grams, depending on the size of the patient. This is repeated in four hours and thereafter a gram is given every four hours until the patient starts to improve. Then the quantity of sulfanilamide is gradually diminished but still continued for three or four days after the temperature has come to normal.

In a disease which varies so much in its severity, in which at one period practically every case results fatally and in which at another period all pa-

tients get well, it is impossible to state definitely that the above form of treatment is unusually effective. In the last three months our results have been perfectly splendid. It might be that we are too optimistic and that in the presence of a more virulent type of meningococcus the results may not prove as satisfactory.

Serum is not used intraspinaly but the spinal canal is drained twice in the first 24 hours, thereafter once or twice in the next 24 hour period and then daily or bidaily, depending on the amount of fluid obtained and the pressure under which it emerges.

I do not think that the physician should weigh too heavily the dangers of active treatment in the case of meningitis irrespective of the bacterial cause. He is dealing with a condition in which the odds are in favor of death. He cannot afford to temporize or to delay. Chances must be taken, which chances incidentally I believe are overstressed. Certainly my experience with sulfanilamide and sulfapyridine have not indicated that more than the very exceptional patient reacts badly to this therapeutic agent.

REFERENCES

1. THENEBE, C. L., HIRSHBERG, M. S., and BOBROW, A.: 350 cases of scarlet fever treated with sulfanilamide and neoprontosil, Connecticut State Med. Soc., 1939, iii, 351.
2. WESSELHOEFT, C., and SMITH, E. C.: The use of sulfanilamide in scarlet fever, New England Jr. Med., 1938, ccxix, 947.
3. FRENCH, J. O.: Effect of sulfanilamide on the blood in scarlet fever, Lancet, 1939, ccxxxvii, 127.
4. CURTIS, W. L.: Sulfanilamide in treatment of tularemia, Jr. Am. Med. Assoc., 1939, cxiii, 294.
5. FRIEDEWALD, W. F., and HUNT, G. A.: The diagnosis of tularemia, Am. Jr. Med. Sci., 1939, cxcvii, 493.
6. KIMMELSTIEL, P., and CALDWELL, H. W.: Tularemic septicemia; report of a case, Am. Jr. Path., 1939, xv, 127.
7. BUNDESON, H. N., FISHBEIN, W. I., and WHITE, J. L.: Diphtheria immunity in Chicago, Jr. Am. Med. Assoc., 1939, cxii, 1919.
8. JONES, F. G., and MOSS, J. M.: Combined diphtheria toxoid and tetanus toxoid, alum precipitated, Jr. Lab. and Clin. Med., 1939, xxiv, 512.
9. HAUSER, G. H., and MUSSER, J. H.: Encephalitis as a complication of measles, Jr. Am. Med. Assoc., 1928, xc, 1267.
10. PETERMAN, M. G., and FOX, M. J.: Postmeasles encephalitis, Am. Jr. Dis. Child., 1939, lvii, 1253.
11. MCKHANN, C. F.: Prevention and modification of measles, Jr. Am. Med. Assoc., 1937, cix, 2034.
12. KOHN, J. L., FISCHER, A. E., and RESCH, H. U.: Treatment of early measles with parenteral whole blood, Jr. Pediat., 1939, xiv, 502.
13. SAUER, L. W.: Immunization against whooping cough, Am. Jr. Dis. Child., 1935, xlix, 69.
14. LUCAS, R. T.: Convalescent serum in the prevention and treatment of common contagious diseases in childhood, New Orleans Med. and Surg. Jr., 1939, xcii, 289.

15. CAMPBELL, E. P.: Chickenpox in a 12 day old infant, *Am. Jr. Dis. Child.*, 1939, lvii, 1408.
16. SHUMAN, H. H.: Varicella in the newborn, *Am. Jr. Dis. Child.*, 1939, lviii, 564.
17. TRIPOLI, C. J., and FADER, D. E.: Acute lymphocytic choriomeningitis with a report of 12 cases from Louisiana, *New Orleans Med. and Surg. Jr.*, 1939, xcii, 308.
18. TOOMEY, J. W.: Acute lymphocytic meningitis, *Jr. Pediat.*, 1936, viii, 148.
19. WALLGREEN, A.: Acute aseptic meningitis, *Acta paediat.*, 1925, iv, 158.
20. TRIPOLI, C. J.: Bacterial meningitis: a comparative study of various therapeutic measures, *Jr. Am. Med. Assoc.*, 1936, cvi, 171.

THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1939

(Seventh Rheumatism Review) *

Part II

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HYPERTROPHIC (OSTEO-) ARTHRITIS

Hypertrophic arthritis was regarded, not as one disease, but as a pathologic "pattern reaction" to different articular insults.^{178, 283} McMurray divided his cases of osteo-arthritis of hips thus: (1) unilateral, those in which a hip was affected by chronic trauma incident to a congenital or acquired malformation, or by single acute trauma; (2) bilateral, those in which both hips were "spontaneously" affected. [We would label the first group "secondary hypertrophic," the second group "primary hypertrophic arthritis."—Ed.] Fletcher listed his cases thus: general osteo-arthritis [i.e., primary hypertrophic arthritis—Ed.], traumatic osteo-arthritis, occupational osteo-arthritis, osteo-arthritis of spine, osteo-arthritis associated with gout, osteo-arthritis leading to infective arthritis [not defined—Ed.], infective arthritis leading to osteo-arthritis [apparently meaning the late hypertrophic changes which may occur in atrophic arthritis.—Ed.]

PRIMARY HYPERTROPHIC (SENESCENT, DEGENERATIVE, OSTEO-) ARTHRITIS

Clinical Data. Joints affected in Monroe's 466 cases were: knees in 60 per cent, fingers in 52 per cent, lumbar vertebrae in 50 per cent, cervical vertebrae in 45 per cent, shoulders in 43 per cent, thoracic vertebrae in 30 per cent, hips in 30 per cent, sacroiliac joints in 30 per cent, "feet (static)" in 15 per cent, temporomandibular joints in 0.5 per cent. Heberden's nodes affected women nine times as often as men in Monroe's series; 93 per cent of Burt's 40 consecutive patients with Heberden's nodes were females. Fingers affected were in order of frequency: right index in 85 per cent of cases, right middle in 58 per cent, left index in 48 per cent, left middle in 43 per cent, right and left "ring finger" each in 38 per cent, and right and left "little finger" each in 33 per cent.

The pain of hypertrophic arthritis has never been adequately explained. The pain of Heberden's nodes is due, according to Bauer⁵⁰ to periosteal elevation from rapid proliferation of marginal osteoid tissue; when the latter occurs slowly, or ceases and marginal osteoid tissue becomes calcified, pain ceases. Other causes of pain are altered mechanics, impingement of pedunculated villus, loose bodies (Bauer), pressure on pain sense organs in bone, vascular congestion in subchondral bone, congestion or edema of irritated synovial tissues (Collins). Stamm distinguished six types of pain in hypertrophic arthritis: (1) that from bone sclerosis which is a deep boring pain unaffected by rest or activity, worse when the part is warm, e.g., at night; (2) that from adhesions and capsular fibrosis which is relieved by rest, aggravated by activity, worse at the day's end; (3) that from nipping of soft parts, a sharp, momentary pain relieved by rest, present only during activity and located at the opposite side of a joint from pain caused by stretching of adhesions; (4) pain from the grinding together of rough surfaces; such pain is present only when movements are made "under load," and is relieved by rest or traction; (5) pain from chronic articular trauma or from associated fibrositis; such pain is associated with stiffness after

resting, relieved by moderate activity, aggravated by more activity; (6) referred pain such as pain in knee from an arthritic hip, sciatica with spinal arthritis.

Premature Hypertrophic Arthritis. Ordinarily hypertrophic arthritis affects only persons over 40 years old, but premature cases are not infrequent. Of Monroe's patients 30 per cent had the disease before the age of 40 years; 12 patients were under 20 years of age. Two unusual cases of premature hypertrophic arthritis were reported.

A girl, aged 15 years, who had marked Heberden's nodes, was noted by Burt; parents were not similarly affected. Polyarticular osteo-arthritis of five years' duration in a man aged 29 years was described by Thomson: hips, knees, shoulders, elbows, wrists and spine were grossly affected; motion was limited but painless; loose bodies were present in shoulders and hip joints [but not elsewhere, hence the case was apparently not one of osteo-arthritis secondary to osteochondromatosis.—Ed.] Thoracic vertebrae showed herniations of nucleus pulposus. Roentgenograms of long bones revealed irregular deformities (fusiform enlargement of femoral and humeral heads, thinning of bone cortex, accentuation of longitudinal striations) suggestive of a disturbance of the growth of the "cartilage-formed bones" rendering them hypersensitive to ordinary stress and strain. From a knee loose bodies were removed and synovia examined: synovial membrane and marginal cartilage were thickened and actively proliferating, chondrophytes being prominent; chronic inflammation and fibrosis were present but no pannus.

[The sedimentation rate was not given. One of us, P. S. H., has seen a similar case: marked hypertrophic polyarthritis of 17 years' duration in a physician aged 34 years, with loose bodies in some joints only; articular motions which were limited, were painless in some, painful in other joints. There has been no loss of weight, flexion deformities or muscle atrophy; sedimentation rates were repeatedly normal. The hypertrophic changes in roentgenograms were marked, resembling those of a senescent patriarch.—Ed.]

Roentgenograms. No new data were reported.

Pathology. This was reviewed by Bauer and Collins.

Laboratory Data. Sedimentation rates are usually normal, occasionally abnormal for unknown reasons^{50, 310}; rates were elevated [degree unstated] in 17 per cent of Fletcher's 103 cases. Serum phosphatase is normal,⁷²⁸ but may be lowered by therapy with vitamin C.⁷⁰⁷ Patients with obvious hypertrophic arthritis who have an elevated serum phosphatase should be examined for malignancy [an important point—Ed.]. Serum proteins are normal or only slightly altered.⁶⁷¹ The average total synovial fluid nucleated cell count is 500; it seldom exceeds 2000 per cubic millimeter; the percentage of polymorphonuclear leukocytes is 10 per cent or less (Bauer).⁵⁰

Etiology: 1. Factor of Tissue Senescence. Collins¹⁷⁸ considered the cartilage changes caused by simple degeneration of advancing years.

2. Factor of Trauma. The wear and tear of long continued trauma was blamed by the majority. "Osteo-arthritic changes in a joint are always and only of mechanical origin" (Stamm). Burt blamed occupational trauma (e.g., needlework, washing), for the production of Heberden's nodes; they "are most often found on the fingers most used." Industrial trauma⁵¹² and abnormal posture⁴³⁰ were also blamed. "The deeper the hip socket, the greater is the proclivity towards osteo-arthritic degeneration" of the hip,

according to Gilmour. A deep hip socket alters the hydrodynamics of the joint; the hydraulic buffer formed by synovial fluid apparently cannot act like a shock absorber, and hypertrophic arthritis develops from mechanical friction.

3. *Factor of Impaired Circulation.* Joints and blood vessels of 13 lower extremities amputated for gangrene from arteriosclerosis of thromboangiitis obliterans were studied by Kling. Synovial vessels were essentially normal; degenerative arthritis was noted only in old joints and bore no relationship to vascular changes; hence the vascular theory was "contradicted."

4. *Factor of Endocrine Dysfunction.* Among Potter's 33 cases metabolic rates were normal in 15, above normal (over + 10 per cent) in five, subnormal (under — 10 per cent) in 13 cases. "Uncorrected rates" were normal for 63 per cent of Rawl's 111 clinic patients, for 43 per cent of 14 private patients; in the rest they were above, oftener than below, normal. Among Monroe's 149 cases metabolic rates were below — 10 per cent in 43 per cent. Bauer⁵¹ noted subnormal rates no oftener than in any group of cases of similar age: "Certainly there exists no proof for the various metabolic, endocrine, circulatory, infectious and toxic theories" of hypertrophic arthritis.⁵⁰ But Kling considered "imbalance and dysfunction of the endocrine system and especially a preponderance of the hypophysis at the menopause" an etiologic factor [no proof given—Ed.].

5. *Factor of Altered Metabolism.* Transient hypertension was not uncommon in Monroe's cases; blood pressure in Weber's cases averaged 142/86 and the mean weight was 162 pounds, 16 pounds more than that of patients with atrophic arthritis. Among 103 cases of "general osteo-arthritis" Fletcher found obesity eight times as often, hypertension four times as often, as in the general sick population. The incidence of hypertension was not wholly dependent on obesity: 37 per cent of the osteo-arthritics of normal weight had hypertension; 42 per cent of the hypertensive arthritics had normal weight. Of the 103 patients 25 were only obese (at least 20 per cent overweight), 26 had obesity and hypertension, 19 had hypertension without obesity. The menopause did not seem to be an important factor. But since obesity and hypertension are presumably related to endocrine abnormalities Fletcher concluded that "an endocrine dyscrasia may be one of the 'triggers' which produce the pattern" of osteo-arthritis.

[This paper, written for the first award of the Heberden medal, is rather disappointing in that it contains little "meat" but much hypothesis, mostly as to the causes of obesity and hypertension rather than of hypertrophic arthritis. As to the influence of the menopause the writer seems to contradict himself, and he seemed to be uncertain of his own conclusions.—Ed.]

No notable abnormalities in sulfur metabolism were found.^{184, 811} Most of the 21 patients of Sherwood and Thomson were on diets deficient in calories, protein and minerals but not in vitamins; despite this the vitamin C content of blood was generally subnormal. According to Traut and Vrtiak

allergic manifestations (asthma, hay fever, urticaria, eczema, migraine, rhinitis) affect patients with hypertrophic arthritis oftener than normal persons or those with atrophic arthritis.

6. *Factor of Infection.* The infective theory was supported by Crowe and his colleagues.²⁰⁷ Based on his studies on streptococcal antibodies Levinthal conceded a relationship to streptococcal infections in some cases of hypertrophic arthritis. But the leukopenic index after intravenous injections of "streptococcal substance" was normal in the cases of Hicks and Wyatt.

7. *Neurogenic Factor.* "The amount of pain and stiffness exhibited by a case of osteo-arthritis depends just as much on the attitude toward life as on the degree of bony or ligamentous change disclosed by the radiograph, perhaps even more" (Gordon). The previously mentioned conclusions of Stein-Lewinson applied to cases of hypertrophic as well as atrophic arthritis. (See Etiology of atrophic arthritis, psychogenic factors.)

Treatment. Weight reduction diets were advised in obese cases.^{32, 386} The supposed value of a raw vegetable, fruit, cereal and milk diet was discussed.⁵⁹⁹ "Vitamins are harmless and may be used if the spiritual support of pills is required."⁵⁴² Vitamin D in concentrated doses was recommended by some.^{693, 707, 758} Injections of sulfur reputedly gave some subjective improvement.^{184, 282, 811} Gold therapy produced no cures, "good results" in 20 per cent, "fair results" in 25 per cent, and poor results in 55 per cent of the 20 cases of Snyder, Traeger and Kelly; others⁶⁵⁰ considered it of little or no value. Results from Crowe's vaccine^{206, 207} were as follows: of 1062 patients treated by Crowe 7 per cent became symptom free, 41 per cent were "much improved," 35 per cent were "improved," 17 per cent were unrelieved. Of Voss's 62 patients so treated 21 were "much improved or cured," 18 improved, 23 unimproved. Weiner considered "specific" and nonspecific vaccines, given without febrile reactions, of doubtful value. Stanley favored the use of chaulmoogra oil. Bee venom seemed valuable to Ainlay but not to Mackenna. Thyroid extract was considered a "valuable adjunct."⁶¹⁶ Fletcher²⁸² tried to reestablish the use of iodine.

[The results given in all of these papers impressed us very little.—Ed.]

Intra-articular injections of lactic acid were recommended by Waugh for reasons already given (see treatment of atrophic arthritis: surgical orthopedic measures); 12 patients with hypertrophic arthritis were "improved" thereby. Stamm recommended roentgen therapy for the deep boring pain presumably caused by bone sclerosis, but reported no results. Local roentgen therapy for peripheral osteo-arthritis, and widefield roentgen therapy for spinal arthritis were again advocated by Scott; results were "very good" for knees, "satisfactory" for smaller joints, "very satisfactory" in cases of spondylitis. [Scott has not yet given his results in statistical percentages.—Ed.] Eidenow noted no real effect from roentgen therapy, only some analgesia.

Fever therapy gave significant relief in only three of Ferderber's eight cases; in 14 per cent of 128 cases of Davison, Lowance and Crowe. It was not recommended by Neymann. Results from acetyl-beta-methylcholine chloride seemed poor to some,⁴⁵³ fair to others.⁹² The advantages of infra-red,⁷⁷⁶ short wave therapy^{113, 197} and fangothrapy⁷⁸⁷ were noted. Proper shoeing, the use of foot plates,⁴⁷⁶ bandages for knees, Thomas heels and exercises for quadriceps muscles were discussed.³⁴⁰ Local injections and regional anesthesia with procaine solutions were strongly recommended by Steinbrocker.

For painful hips Green³⁴⁰ and Stamm considered traction at night useful, but according to Fisher the pain in hypertrophic arthritis is due generally to contractures of capsule and periarticular tissues, rarely to apposition of articular surfaces; hence caliper splints and other measures to separate articular surfaces are rarely indicated.

Manipulation had its advocates.^{57, 58, 278, 529, 594, 723} Stamm used it (under anesthesia) to relieve pain due to adhesions, capsular fibrosis and to nipping of soft parts; others used it for painful stiff hips,^{278, 529, 594} but Douthwaite saw no rationale to it; in his opinion it generally does not relieve affected hips but may relieve associated fibrositis. Complete relief of pain was provided by Burns in eight of 12 cases of hypertrophic arthritis of hips by fixation with a Smith-Petersen pin; a method of performing this operation without exposure of the joint was described.³⁰ Since synovial membrane is rarely much affected in hypertrophic arthritis, synovectomy is indicated only in late cases if the membrane is thickened and thrown into folds at the periphery of the joint; partial synovectomy to remove papillary masses of granulation tissue may then relieve pain and improve function (Swett). In three cases of hypertrophic arthritis of knees excision of patellae was done by Berkheiser with apparent improved function. Selig recommended arthrodesis in some cases when one hip is affected, unilateral osteotomy for a patient with both hips affected who refuses fusion of one; he considered arthroplasty of hips inferior to fusion; acetabuloplasty and drilling (forage) were considered of uncertain value.

Since degenerating cartilage is never replaced by normal cartilage a cure of hypertrophic arthritis is impossible.^{50, 542} "The disease stops only with death," but the foregoing measures may retard the process, relieve pain and improve function. Monroe's follow-up study of 331 cases showed "good results" in 53 per cent, "improvement" in 32 per cent, no results in 15 per cent.

BACKACHE AND SCIATICA

General Remarks on the Causes of Backache and Sciatica. The literature under review included almost 100 papers on these subjects, among them general articles on the causes of backache, the technic of examining patients therewith,^{290, 295, 420, 457, 553, 680, 791} and the special roentgenographic examina-

tions often required.^{61, 151, 349} A roentgenographic study of spinal mobility was made by Elward who suggested revision of some current ideas thereon. It was disproved that flexion is freest in the lumbar region. The spinal column is not a single hinge but many interacting hinges; there is no single center of motion, except the mass motion of flexion centering in hips; there are numerous centers of limited motion. Structures of the back are so inter-related that disease of one may produce disease in another; hence several different conditions may produce rather similar symptom complexes. Differentiation can only be made by careful physical and roentgenologic examinations; no one orthopedic maneuver or "test" is pathognomonic of one spinal condition.^{231, 290}

Physicians again disagreed as to which are the commonest causes of backache. Some⁴²⁷ said strain; others⁵⁵³ incriminated arthritis, poor posture and trauma in that order. Owen's order of indictment was infections, acute or chronic trauma, poor posture, congenital anomalies and intraspinal lesions (herniated disks, tumors, fractures).

Backache from Urologic Lesions. No data thereon came under review.

Backache from Gynecologic Lesions. No new data were reported.

Backache from Gastrointestinal Disease. Back pain caused by peptic ulcer, gastric cancer and diseases of gall-bladder, liver, pancreas, appendix and colon were briefly distinguished: in general the eating of food affects this type of pain.⁵⁴⁵

Backache from Disease of Interspinal Ligaments. The interspinal ligaments connect adjoining spinous processes; they are stretched in flexion and function constantly. Macey described an unreported type of backache, a localized painful region between two or more spinous processes; pain was aggravated by flexion and not relieved by usual conservative therapy—heat, massage, etc. Tenderness to pressure was superficial; roentgenographic, neurologic and orthopedic examinations were negative. In one case of five years' duration, pain began after the strain of childbirth. A diagnosis of chronic localized interspinal ligamentitis was made and supported by the temporary relief of pain when the affected ligament was injected with 15 to 20 c.c. of 1 per cent solution of procaine. Operative removal of the affected tissue gave complete relief; the ligament showed chiefly degenerative changes with some nests of inflammatory cells, mostly lymphocytes. Kleinberg⁴⁵⁹ described acute traumatic disease of interspinous ligaments.

"*The Dorsolumbar Syndrome*": "*First Lumbar Nerve Neuralgia*." A "new syndrome" was reported, called the "dorsolumbar syndrome" by Judovich and Bates, "first lumbar nerve neuralgia" by Tarsy, "causalgia of the twelfth dorsal and first lumbar nerves" by Hudson and Hettesheimer. Studies of Judovich and Bates indicated that the distribution of the twelfth dorsal and first lumbar nerves is much wider than supposed and overlaps lumbosacral and sacro-iliac regions. For certain anatomic reasons the nerves are frequently irritated at the dorsolumbar joint; a common and charac-

teristic backache results with tenderness and pain along the distribution of affected nerves. In cases of Hudson and Hettesheimer unilateral pain extended over the lower back, iliac crest or midlumbar region with hyperesthesia of skin supplied by the twelfth dorsal and first lumbar nerves. Pain and tenderness were referred anteriorly over the abdomen⁴³⁴ and in some cases led to abdominal operations. Rapid relief was afforded by perineural injections,⁴³⁴ or by injections of 1 per cent solution of procaine or of eucupine in oil which presumably broke up adhesions and separated fascial spaces.⁷⁵³ Others⁴¹³ recommended removal of foci, correction of pelvic tilt with an elevated heel on the abducted side, and exercise to strengthen the abdominal and weaken the sacrospinalis muscles.

In some of Hudson's cases backache was minor, but abdominal pain was "intractable"—burning, boring or aching pain in either lower quadrant, aggravated by motion; it wakened patients at night and was relieved by sitting up. Pain was elicited by pressure upward over the eleventh and twelfth ribs and over the transverse processes of the eleventh and twelfth dorsal and first lumbar vertebrae. Unrelieved by abdominal explorations, the pain was relieved within two hours to two weeks by paravertebral sympathetic block with procaine; in some cases alcohol injections gave relief for a year but transient alcoholic neuritis sometimes resulted.

Backache from Tight Fascia Lata and Iliotibial Band. The syndrome was again described and indications for conservative or surgical treatment were outlined. Ober's sign is not always positive even when the iliotibial fascia is tense.³³⁹ Fasciotomy gave good results in 45 per cent of Heyman's 12 cases, in 70 per cent of Logue's 10 cases, in 75 per cent of Smith's⁷⁰¹ cases, in 90 per cent of Green and Gondy's 20 cases. Fasciotomy was done by Nutter in 45 cases with success in 70 per cent of the 35 cases of sciatica with backache, in 67 per cent of three cases of sciatica without backache, in 43 per cent of seven cases of low back pain without sciatica. Fasciotomy was not satisfactory to Mumford and Reynolds. Several patients unrelieved by fasciotomy for presumed tight fascia lata were later relieved when Bradford and Spurling removed herniated disks. A "successful" conservative method was reported by Ilfeld—a new method of strapping thigh and back; of 11 patients so treated five obtained "excellent," six satisfactory results.

Sacro-iliac Backache and Sciatica from Lesions of the Piriformis Muscle. Smith⁷⁰¹ did not advocate cutting the piriformis for this supposed condition.

Backache from Developmental Anomalies. According to Dittrich spina bifida occulta is often associated with intraspinal pathologic changes, masses of fibro-adipose tissue overlying the dural sac and sacral nerve roots with fibrous cords extending between the ventral surfaces of the laminae and the dura or nerve roots. Mechanical irritation of nerves, muscle tenderness in lower back and legs, and absent or diminished knee and ankle jerks result. Laminectomy and removal of abnormal tissue was done in seven cases of "muscular rheumatism" with spina bifida; in all relief was complete. Craig

and Walsh warned that developmental anomalies are often benign and not the cause of the backache; they were frequent among 300 cases of backache relieved only by removal of protruded intervertebral disks.

Spondylolisthesis. Anterior spondylolisthesis affected five of 75 cadavers.⁴⁰⁰ Many cases are symptomless and need no treatment.⁴⁵⁷ Current writers^{409, 439, 457, 459, 472, 550} regarded the condition as a developmental defect made symptomatic by trauma. In Kark's case, trauma alone produced the condition. A child 18 months old with the condition was mentioned.^{457, 459} Conservative therapy was usually advised: rest in bed, then temporary support with belt, plaster corset or brace,⁴⁵⁷ reduction of the deformity by applying slings⁴³⁹ and traction.⁴⁷² For intractable cases fusion was recommended. George's results were: of 50 patients treated conservatively only 18 per cent obtained complete relief; 20 per cent partial relief, the rest no relief; of 91 patients treated by Hibb's fusion 81 per cent obtained complete relief. But conservative therapy was successful in "at least 75 per cent" of the cases of Krusen and Basom.

Reverse Spondylolisthesis. Horwitz⁴⁰⁰ noted posterior displacements of from $\frac{1}{8}$ to $\frac{1}{4}$ of an inch in nine of 75 cadavers studied.

Prespondylolisthesis: "Spondylolysis." Kleinberg^{457, 460} defined this condition as the existence of a congenital laminar defect in a lower lumbar vertebra or on one or both pedicles of the affected vertebrae, separating the articular facets by a distinct gap, a condition predisposing to future spondylolisthesis. Low back pain with or without sciatica may or may not result. George reported 42 cases of "spondylolysis."

The Facet Syndrome: Arthritis of Facets. No new data were reported.

Coccydynia. This may result from spasm of levator ani, coccygeus or pyriformis muscles, and may produce not only coccygeal, but also sciatic or supragluteal, pain. Krusen and Basom recommended heat and internal (intra-rectal) massage after the method of Thiele, 1937 (technic given).

Diseases of Intervertebral Disks. Lesions of disks, not necessarily protrusions, were considered by some⁴³ the commonest single cause of low back pain with sciatica. Various lesions were again discussed: senile degeneration, lesions from trauma, spinal puncture needling, infections, calcification of disks, healing after injury, and those producing adolescent and senile kyphosis.⁶⁵¹ The anatomy and physiology of disks and related structures were described, also lesions of disks found in cadavers.^{233, 400}

1. Senile Fragmentation. Degenerative changes in disks from aging and wear and tear may produce kyphosis not only in the elderly, but in young persons with congenital weakness of cartilage plates.²³³ Among 75 persons, aged 45 to 80 years at time of death, narrowed disks with fibrillation of fibrocartilage and dehydration of nucleus pulposus were found between the fifth lumbar and first sacral vertebra in 50, between other lumbar vertebrae less often.⁴⁰⁰

2. Ruptured Intervertebral Disks. So "popular" is this subject that it

comprised a third (35 papers) of all current reports on backache under review; most noteworthy were those of Bradford and Spurling, Barr, Craig and Walsh, Fincher, and Love. In 6 per cent of 50 cadavers Batts noted anterior protrusions of disks, in 20 per cent protrusions into vertebral bodies, in 16 per cent posterior protrusions. Frank posterior protrusions were found by Horwitz⁴⁰⁰ in only four of 75 cadavers. The relative importance of ruptured posteriorly protruding disks as a cause of backache and sciatica has not yet been established. Some consider them the commonest cause of low back pain with sciatica; thus of Adson's 60 patients who underwent operations for that complaint 35 had herniated disks. Posterior protrusions of disks complicated 42 of Olin's 50 cases of fractured vertebrae. A dozen papers detailed the clinical features of over 600 cases of protruded disks proved at operation to be the cause of low back pain generally with sciatica. Some of the 600 cases were continuing series partly reported previously: thus 300 cases were reported from the Mayo Clinic,^{201, 499, 793} but it was emphasized that this large number accepted for such surgical treatment were only about 2 per cent of 13,000 cases of low back pain with sciatica seen by orthopedists of that Clinic during the same three year period.^{201, 378, 499}

Etiology. A history of trauma was found as follows: recent trauma in 37²⁰¹ to 50 per cent,⁴⁵ remote trauma in 22²⁰¹ to 30 per cent,⁴⁵ no known trauma in 17,⁹⁰ 20⁴⁵ and 41 per cent²⁰¹ of cases. As in previous series the greatest frequency of the protrusions was between the fourth and fifth lumbar or the lumbosacral bodies.^{11, 45, 90, 93, 201, 499, 793} Among the 300 cases of Craig and Walsh lesions were lumbar in 285, cervical or thoracic in only 15. In the Mayo Clinic series protrusions were multiple in about 10 per cent.^{201, 499, 500} From 70⁹³ to 75 per cent^{90, 201} of the patients were men.

Symptoms. Many herniated disks produce no symptoms but are obvious only roentgenographically; such require no treatment. Symptoms when present consist of root pains generally involving lumbar, sacral and sciatic regions. They are *not pathognomonic* but simulate those produced by several syndromes. Sciatica was unilateral in 85 per cent, bilateral in 15 per cent of one series of cases.²⁰¹ Neurologic examinations were entirely negative in 6 per cent of the series, and in 15 per cent more they were negative except for a positive Lasègue's sign and/or sciatica.²⁰¹ But usually a characteristic clinical syndrome is present. Reflexes may be normal^{11, 480} but usually are not.^{720, 721, 722} The Achilles reflex was abnormal in 43 to 50 per cent of cases.^{45, 93} In all Barr's cases positive Lasègue's signs were present, in 90 per cent reversal of lumbar curve, in 60 per cent sciatic scoliosis, in 35 per cent sensory changes in extremities, in 15 per cent motor changes (weakness, palsy), in 5 per cent sphincter disturbances, in 50 per cent local tenderness over the affected lumbar spinous processes (also in 50 per cent of Fincher's cases), in 40 per cent root pains on coughing, sneezing or jugular compression. Other analyses of symptoms were given.^{93, 201} In one group only 5 per cent of patients had sciatica *without* low back pain.²⁰¹

Among Barr's cases symptoms were constant in 60 per cent, intermittent in 40 per cent (they were intermittent in 81 per cent of the cases of Craig and Walsh). In one case²⁰ of protruded disk a meningitic cyst (circumscribed arachnoiditis) was produced by mechanical irritation from the disk protrusion; in some cases pain may be caused, not by the disk, but by associated inflammatory processes.

Diagnosis. Ordinary spinal roentgenograms in cases of protruded disks may or may not be helpful; they often reveal what is *not* the cause of pain, e.g., osteophytes, developmental defects, narrowed intervertebral spaces without protrusions.^{90, 93}

But narrowed spaces corresponding to the neurologic level of pain are suggestive evidence of a damaged disk with protrusion.^{11, 45, 500} Spinal fluid protein is usually increased, but is sometimes normal^{43, 90, 480}; it was under 40 mg. in from 11 to 25 per cent of cases,^{11, 93} over 40 mg. in 66 to 85 per cent of cases.^{11, 45, 201} When spinal fluid protein is normal, the reversed Queckenstedt test is a valuable sign¹¹ and should be positive before spinograms are done.

Air myelography (pneumospinograms, airograms) is much less dangerous than myelography with lipiodol, and was preferred by some^{161, 272}; if results therewith were doubtful, spinograms with lipiodol were made. The technic of air myelography was described.^{136, 201} Most physicians agreed that air myelograms were satisfactory in cases of complete spinal block but were generally quite inferior to those with lipiodol and not to be relied on.^{106, 136, 218, 546, 643, 675, 697, 701} The technic of spinograms with lipiodol was described^{90, 136} and the diagnosis was predicted accurately in 92 per cent of 210 cases. Although some physicians insisted that 2 c.c. of lipiodol were enough,^{93, 454} the majority considered 5 c.c. necessary for accuracy^{11, 45, 136, 500, 651} and noted no notable reactions.^{45, 272, 697} Bosworth and Hare noted fresh intradural adhesions two or three days after injection of lipiodol; Mumford and Reynolds noted severe reactions in "at least half" of their 13 cases in which lipiodol was used. All writers agreed that such spinograms should never be made indiscriminately, but only after careful preliminary general, neurologic and orthopedic examinations, and the oil should be removed surgically. Because of objections to such spinograms some physicians, on the basis of increased clinical experience with the characteristic findings, performed laminectomy without the use of lipiodol injections.^{501, 675}

In summary, patients with recurring low back pain and sciatica with or without a definite history of trauma, with exaggerated spinal flexion or torsion, a positive Kernig or Lasègue's sign, diminished Achilles reflexes and an increased protein in the spinal fluid should be suspected of having a protruded disk and myelograms should be made after injection of air or lipiodol.¹¹

Pathology. The extruded material does not represent chondromas, as was once believed, but consists of all the parts normally found in unprotruded disks. The tissues are altered: present are degeneration of cartilage cells (more often than of fibrils), proliferation of fibrous tissue and edema of protruded tissues. Variability in the edema may account for the intermittency of symptoms.²²¹

Treatment. Facetectomy alone was considered inadequate.^{200, 201} Surgical technic for laminectomy and removal of the protruded disk was described.^{11, 45, 200, 272, 499, 500, 720} The radiopaque oil should be removed: a special method for this was suggested.⁵⁸⁰ The hypertrophied ligamenta flava so often found should also be removed. Laminectomy should not be done until conservative therapy (rest in bed, heat, traction) has failed and the sciatica has become recurrent, because conservative measures may reduce small protrusions.^{11, 720} Manipulation may relieve pain by stretching and paralyzing involved nerve roots but is inadvisable because it may precipitate paraplegia.⁴⁵ Some physicians^{45, 106, 701} advocated bone graft at the conclusion of laminectomy; others with large experience considered it rarely if ever necessary.^{11, 378, 675}

Results of Treatment. Immediate results of laminectomy were usually excellent. Almost every one of Barr's 83 patients noted immediate relief; there were three failures, two deaths. Of 18 other patients, 15 were relieved; one died.⁹⁰ Among 35 cases of Bradford and Spurling results were excellent in 26, good in seven; there were two deaths, one postoperatively, one late. Pain recurred in one case until arachnoidal adhesions were removed. Among Fincher's 50 cases, relief was complete in 80 per cent, partial in 10 per cent, not obtained in 10 per cent; there were no deaths. The largest series was that of the Mayo Clinic: results among 300 cases were generally excellent; one patient had a nonfatal postoperative hemorrhage; only one of the 300 patients died (infected wound and bronchopneumonia).^{201, 499, 500, 501} It is too early to evaluate results finally or to determine the number of late recurrences.

Only one writer jarred the harmony of these reports. Pappworth caustically criticized the members of one Boston group, pointing out apparent contradictions and discrepancies in their various papers. He suggested that the rest in bed and not the laminectomy may have been the cause of relief in many cases, and advocated "a closed season" on the writing of papers on this subject until a more judicious appraisal of late results can be made. He was unable to believe that the symptoms were due chiefly to the protruded material but suggested that many of the protrusions were incidental findings.

[The best answer to this criticism is the insistence of the writers that most of the patients treated surgically had failed to respond to prolonged conservative and "nonsurgical" treatments including rest in bed, and one orthopedist³⁷⁸ agreed that results from laminectomy are far superior to those attained by older surgical or nonsurgical orthopedic measures.—Ed.]

Backache and Sciatica from Hypertrophied Ligamenta Flava. Hypertrophy of these ligaments often accompanies ruptured disks: the trauma which ruptures the disk also tears the ligamenta flava which hypertrophy during healing.^{11, 480} Hypertrophied ligamenta flava were found by Craig and Walsh in 155 of their last 175 cases of protruded disks. Such hypertrophy often occurs alone, perhaps from localized extradural hemorrhage producing fibrosis and thickening.⁴⁵ Symptoms are usually low back pain with sciatica; signs resemble those from ruptured disks.^{546, 766} In one case⁹³ there was no pain, but trophic ulcer of heel, incontinence of urine and feces,

and saddle anesthesia were noted. Among 75 cadavers Horwitz⁴⁰⁰ found no pressure on caudal nerve roots from hypertrophied ligamenta flava. Treatment involves laminectomy and removal of the hypertrophied disks.¹⁶¹ Of 13 cases of Bradford and Spurling late results were: complete relief in eight, postoperative death in one, much relief but slight residual pain in four cases.

Backache from Senile Osteoporosis. Elderly persons, usually females, often present stiff, tender spines with marked osteoporosis, reduction in size of vertebral bodies, and increased dorsal curve. The cause is unknown; no known chemical abnormality is present in blood.^{238, 457} Recommended were complete rest from weight bearing for two to three months, then physical therapy and a brace.

[Albright and colleagues called this condition "post-menopausal osteoporosis" and recommended estrin therapy to produce a positive calcium balance.—Ed.]

Miscellaneous Conditions of the Spine. 1. *Malignancy.* Among 60 patients operated upon for low back pain with sciatica three had spinal malignancy.⁹³ In one case sciatica was caused by prostatic carcinoma; therefore, rectal examinations should be done in all cases of sciatica.⁷⁶² For intractable spinal malignancy Love⁴⁰⁹ advised sedatives and injections of alcohol into the subarachnoid space.

2. *Rickets of the Spinal Column.* Roentgenologic features were described (Oppenheimer).

Myofasciitis of the Back: Lumbago. Acute lumbago or lumbar myofasciitis supposedly is caused usually by sprains, but of this there is often no pathologic proof; hence Makaroff blamed acute vasospastic disorders related, perhaps, to small emboli from distant foci [no proof given.—Ed.]. According to Albee and Campos myofasciitis, a "toxic inflammation or metabolic change of muscles and their associated fasciae," is the commonest cause of low back pain. Among 1188 cases trauma was a factor in only 25 per cent. They blamed the condition on infected foci, constipation with an "elevated histamine index of the stools," uric acid retention, nervous strain or vitamin deficiency and allergy [or what have you! No proof for these ideas was given.—Ed.].

The pathologic basis of lumbago is unknown; in most cases none can be demonstrated, but in two of Kleinberg's⁴⁵⁷ cases biopsies revealed inflammation of gluteus medius muscle, in three cases hyaline degeneration.⁴⁵⁹ According to Albee and Campos subcutaneous nodules contain a gelatinous substance infiltrated with leukocytes, sometimes round cells [no specimens shown.—Ed.].

Albee and Campos again described the "myofasciitis (leg-raising) test." Although roentgenograms were "negative," Albee and Campos considered myofasciitis a "pre-arthritis condition" which, neglected, may lead to arthritis. Despite the uncertain pathology of the condition Heyman stated that the lumbar fascia is often thick and taut: the most important diagnostic

sign was localized tenderness at or near the posterior superior spine plus painful forward bending and straight leg-raising.

Treatment. Conservative measures included rest and physical therapy. Others recommended fasciotomy with or without muscle stripping.^{384, 457} According to Gorrell lumbago "can often be relieved in five minutes, cured in an hour" by injecting 10 to 25 c.c. nupercaine solution into "trigger points" and then prescribing immediate active *use*, not rest, of muscles; he cited 13 cases of relief from one or two injections. Nupercaine often produced transient vertigo; the effect of procaine was too transient.

Postural Backache. Many writers included this under "lumbosacral strain," others^{457, 720} considered it a separate entity. Faulty posture may produce low back pain with a true sciatic endoneuritis or perineuritis. For patients not relieved by conservative means (proper shoes, postural exercises) epidural endosacral and endoneural injections of procaine, or nerve-stretching were used.⁷²⁰

Lumbosacral and Sacro-Iliac Backache and Strain. Under this vague heading physicians described and treated many cases of acute or chronic low back pain. In 96 per cent of the cases of Mumford and Reynolds caused by "effort strain from indirect trauma," relief occurred within one to four weeks from "almost any treatment." Recommended were good adhesive strapping, rest in bed with knees flexed, after five days removal of adhesive tape and use of physical therapy. Epidural injections, manipulations, casts and corsets had not given relief.

"Lumbosacral sprain." Goff described his technic for finding the "trigger point," the chief site of strain, and curing it by intramuscular, or if necessary by epidural injections of procaine.

"Sacro-iliac sprain." This is rare according to some,^{420, 701} common according to others. It can be demonstrated unmistakably in roentgenograms according to Chamberlain; roentgenograms may show hazy sacro-iliac joints from acute effusions within 24 hours after injury⁴⁵⁹ and such sprains are the commonest cause of "industrial backaches." Recommended were long protection of the back with plaster jackets, later corsets, physical therapy and graded exercises; for stubborn cases manipulation without anesthesia (technic given)⁴¹⁴ or arthrodesis.⁴⁵⁹

Unclassified "Low Back Pain" with or without Sciatica. Manipulation without anesthesia was recommended.^{414, 432} [The technic was given; apparently the presence of sprain was implied.—Ed.] Others used local injections of eucupine in oil,⁴²⁰ postural exercises and supports, rarely fusion.⁴²⁷

Additional Comments on the Treatment of "Backache and Sciatica." In 90 per cent of cases in which no more specific diagnosis can be made, conservative measures give relief; in 10 per cent or less fusion is needed.^{94, 577, 759} Conservative measures included rest, traction, hot applications, later braces or plaster shells, spinal massage, postural exercises.^{43, 106, 370, 630, 759} Local or regional injections of procaine or eucupine in oil were also used.^{290, 730, 753}

Sciatica: Additional Comments. Comments on the classic of Cotunnus were made.²⁸ Harris classified sciatica thus: (1) high sciatica from lesions near intervertebral foramina around the fourth and fifth lumbar nerves caused by osteo-arthritis, septic inflammation or rheumatic disease (e.g., fibrositic sciatic perineuritis); Achilles jerks are normal, the patient often leans away from the affected side; (2) low sciatica caused by lesions near the sciatic notch, a true "toxic neuritis" from lead, arsenic, diabetes, an infective neuritis from infected foci, a traumatic neuritis or one from direct

chill to the buttock; the Achilles jerk is often lost and the patient leans toward the affected side. According to Burt there is (1) root or high sciatica, (2) trunk (low or true) sciatica, and (3) referred sciatica from arthritis, bursitis, fibrositis. Of his 140 cases of "rheumatic sciatica" 35.5 per cent were of the root, 17 per cent trunk and 45.5 per cent referred type. [This equals 98 per cent.—Ed.]. A pathologic specimen of trunk sciatica (microphotographs) showed exudative swelling and thickening of the epineurium, engorgement of blood vessels and perivascular lymphocytic exudate; organization of exudate leads to formation of adhesions. Wagoner reported cases of sciatica from fibrous adhesions about the nerve, relieved completely by surgical removal of the constricting fibrous tissue. The causes and treatment of sciatic scoliosis were discussed.^{457, 459} The intrathecal use of alcohol for sciatica is dangerous; it should be employed only in cases of intractable pain from malignancy, but in such cases chordotomy was preferred.^{457, 459} Bilateral sciatica is more serious than unilateral sciatica and generally indicates intraspinal lesion, tumor or malignancy.¹⁰¹ For trunk sciatica rest, heat, injections of saline into and around the sciatic sheath and, if necessary, nerve stretching under anesthesia were recommended; massage was condemned.^{127, 367, 657} If acute sciatica fails to improve under such treatment or pain increases, an intraspinal lesion requiring laminectomy is usually present.²⁰⁰

* ATROPHIC (ANKYLOSING) SPONDYLITIS

Clinical Data. Data on two new series of cases were reported.^{285, 742} Sex incidence in Swaim's 106 cases was 84 males, 22 females; the ratio may be as high as 20 males to one female.⁵¹ In over 80 per cent of Forestier's cases the condition had escaped diagnosis during its first three years when only vague pains of lower back or chest were present. Small joints of only five of Swaim's 84 males were affected.

Laboratory Data. Sedimentation rates are usually high, sometimes higher than in peripheral atrophic arthritis.³¹⁰

Roentgenograms. For early diagnosis it is most important to know that the earliest roentgenographic changes almost always affect sacro-iliac joints,^{151, 285, 669, 742} but projections from several angles may be required to demonstrate sacro-iliac and intervertebral changes. Sacro-iliac joints were not involved in only two of Forestier's 153 cases. He described the various roentgenographic stages of the "sacro-ileitis": first stage, periarticular marginal decalcification; second stage, pyknotic formation, giving a mottled appearance, with both decalcification and hypercalcification; third or terminal stage, total fusion with fibrillary ossification and regions of osteosclerosis. When only a few small regions of intervertebral ligamentous calcification are present, they may be confused with osteophytes. According to Forestier the former, "syndesmophytes," can be differentiated easily from osteophytes from the beginning: the former appear as a wooly shadow in the inter-

vertebral space; in a few months a rather clear-cut, dense, linear area of calcification without a cortex appears which looks like a thin or thick comma on the vertebral body; osteophytes have a much thicker base, are covered with a cortex arising from that of the vertebral body, and a structure of cancellous bone like the vertebral body itself.

Etiology. In 60 per cent of Forestier's cases genito-urinary infections, not necessarily specific, were present; perhaps toxic products from the male genito-urinary tract spread via pelvic lymphatics to spine; in women the lymphatic spread from pelvic organs does not approach the iliac joints.³⁴

Treatment. The usual medical and orthopedic remedies were reviewed.⁴⁴⁷ Such a program (hyperextension in bed, use of plaster half-shells, physical therapy, corrective exercises, then braces) gave results unsatisfactory to Swaim: in 35 of 45 cases in which this treatment was used affected vertebrae fused completely in 35, in 31 posture remained poor, in 21 motion of the hips was lost; death from pulmonary infections occurred in nine cases. A superior plan was evolved: preliminary correction of spinal deformity by hyperextension in bed for two weeks, then the application of a plaster jacket "for early, continuous and adequate immobilization." Jackets were left on for weeks, replaced by new ones as posture improved; they were worn by 62 patients for from months to nine years. Muscle spasm and pain were rapidly relieved, sleep improved markedly despite the jacket, deformities were prevented or improved notably, expansion of the chest and weight increased. No new hip trouble occurred and vertebral bridging was definitely retarded.

Chrysotherapy in conjunction with intramuscular or intravenous injections of thorium-X or radon was highly recommended by Forestier: 80 per cent of 25 patients became symptom free within two years. Bach also recommended chrysotherapy but it disappointed others^{447, 452} as did fever therapy.¹⁰² Kersley advocated deep roentgen therapy to relieve sacro-iliac pain. But neither deep nor short wave length roentgen-rays should be used "under any circumstances" according to Scott who extolled the virtues of widefield irradiation which sometimes gave "spectacular results." Others²⁵⁰ did not share Scott's enthusiasm.

HYPERTROPHIC SPONDYLITIS (OSTEO-ARTHRITICA)

Clinical Data. Marginal vertebral osteophytes have too long masqueraded as hypertrophic spondylitis; when present they may not be the cause of a patient's pain, according to Chamberlain who preferred Kienbock's term "trophostatic osteoarthrosis." Hartsock described headaches from cervical hypertrophic spondylitis: apparently first occipital, then temporal, they really originated in the cervical region; muscular tenderness at the trapezius attachment to the skull was important in diagnosis; they were precipitated by damp and drafts, aggravated by flexion of neck and lasted longer than attacks of migraine.

Etiology. Spinal hypertrophic arthritis is now generally regarded as merely a phase of "discogenetic disease": age and trauma produce degeneration of disks (not necessarily with herniation), partial luxation of vertebral bodies, narrowing of intervertebral foramina with production of root pains, and irritation of marginal bone of vertebral bodies with osteophyte formation.^{43, 233, 579, 651} The importance of industrial trauma as a provoking and aggravating factor of hypertrophic spondylitis was stressed.^{286, 295, 512, 584, 596} When an Ohio worker over 40 years old with symptomless, perhaps unsuspected, hypertrophic spondylitis falls down, the cost to his employer is likely to be about \$3000, according to Papurt. Such cases are costly to industry, but industry must absorb the cost. Routine roentgenograms of elderly workers are not worth the cost and, if done, would result in an "employment junk heap."

Treatment. One writer¹⁵⁰ considered removal of foci useful. In cases precipitated by industrial trauma prompt rest in bed is better than frequent traumatizing trips to a physical therapist's office.⁵¹² [Solution: have the physical therapist go to the patient's bedside.—Ed.] The associated fibrositis requires heat and massage but not exercises⁴⁴⁷; manipulation may afford relief.³⁸⁶ Patients with cervical osteo-arthritis should wear woolen neck protectors to avoid drafts, especially at night.³⁶⁹ Also recommended were head sling, soft rubber heels to prevent jarring when walking, and cervical traction by the method of Hanflig (1936).⁴⁷² Of 38 patients treated by such traction all obtained some relief.⁷⁵⁸

GOUT AND GOUTY ARTHRITIS

The number of papers on gout was fewer in 1939 than in 1938. The informative article of Brøchner-Mortensen¹⁰⁰ should interest all students of the disease. It gave a detailed analysis of 30 cases with careful studies on excretion of uric acid. Other papers added singularly little to our knowledge of the condition. Some¹²⁸ complained: "Although a whole day was devoted to gout at the recent International Congress on Rheumatic Diseases no startlingly new contributions emerged."

Incidence. The usual controversy about the relative frequency or infrequency of gout prevailed. According to Tolstoi, "The problem is not of tremendous importance in this country as statistics have shown that gout is a relatively rare disease." He quoted statistics to show that the current incidence of gout does not compare with that many years ago.

Futcher observed 124 cases of gout among 53,012 medical admissions to Johns Hopkins Hospital. Between 1903 and 1916 gout was diagnosed only 42 times among 298,500 patients at the Massachusetts General Hospital (Pratt, 1923). At the New York Hospital gout was diagnosed only eight times among 177,000 patients in five years. Gudzent and Holzman found 76 cases among 32,089 postmortem examinations. According to Brøchner-Mortensen¹⁰⁰ the incidence of gout has diminished since 1914. He attributed recent "increases" in incidence to an "unjustified" broadening of the diagnostic criteria. Other reports⁷⁵⁹ supported Hench's claim that "it is the suspicion

of gout, not the disease, which has disappeared." Thus among 2500 patients, Wade observed five with gout, an incidence of 0.2 per cent.

[Some find it difficult to explain variations in statistics on the incidence of gout. Those who believe that the diagnostic criteria are reasonably well standardized must conclude that the incidence varies notably in different countries, even in different parts of the same country. The social level of the clinical material under observation may be an important determining factor; many more cases of gout are seen in private practice than in the large arthritis clinics of the great metropolitan hospitals; others believe that the supposed variations in incidence simply reflect different diagnostic standards for gout in different localities.—Ed.]

Factors Governing Incidence: 1. Heredity. Heredity is generally considered a contributing factor. But Brøchner-Mortensen found a hereditary factor in only one of his 30 cases. After evaluating such factors as alcohol, overeating, lack of exercise, "animal diet," severe study, mental anxiety and exposure to lead, Tolstoi concluded that "the only positive evidence related to the causation of gout is heredity."

2. *Sex.* The usual marked preponderance of males was present in the one series¹⁰⁰ reported which included 29 males and one female.

3. *Age.* The same series gave the age of onset of the first attack as follows: 10 to 20 years in one case; 20 to 30 in two; 30 to 40 in seven; 40 to 50 in 10; 50 to 60 in five; 60 to 70 in four; doubtful in one. The patients' average age at the first attack was 45 years.

4. *Dietary Habits.* Only a few abstainers with gout were noted by Brøchner-Mortensen. Eighteen of the 30 consumed much alcohol, especially beer. "Diet may play some rôle but the character of the [offending] diet has not been determined."⁷⁷¹

5. *Geography and Race.* The disease is unknown in China, Japan and the tropics; Russians, Poles, Swedes and Danes are comparatively immune.⁷⁷¹

Clinical Data: 1. Provocatives. Further comments on the provocative effect of diets high in fat, low in carbohydrates and protein were made by Lockie. Such a diet provoked attacks of acute gouty arthritis in five of Lockie's cases, nine out of the 10 times it was used. But Brøchner-Mortensen was unable thereby to provoke attacks in four cases and concluded that Lockie's test was of no diagnostic value.

Certain foods low in purines (e.g., strawberries) may provoke attacks.⁴¹⁰ The provocative effect of salyrgan diuresis on five gouty patients was again⁶ reported by Price.

2. *Tophi.* Tophi, verified by the murexid test, were noted in seven of the 30 cases of Brøchner-Mortensen; roentgenographic defects resembling tophi were present in 13 other cases.

3. *Unusual Clinical Features.* A case of erythremia with gout and sub-leukemic myelosis⁶²⁴ and one of gout producing ankylosis of multiple joints were reported.¹⁴⁴ A patient who may have had both gouty and tuberculous arthritis was noted.⁵¹²

Irregular Gout (Atypical Gout, Retrocedent Gout). Brøchner-Mortensen advised caution in diagnosing gout in the absence of acute attacks, tophi and hyperuricemia. But Edgecombe defended the idea of "irregular gout" which McKay attributed to the presence of allergy and gout.

According to McKay, allergy and gout, combined in an individual, may give rise to a distinct variety of gout not previously recognized. Irregular gout occurs among those who possess a gouty diathesis plus an allergic constitution. The following symptoms were supposedly due to "allergy-gout": cutaneous eruptions, nervous mani-

festations, diseases of the eye and eyelid, nasal affections, "run-away heart," and certain gastrointestinal and bronchial symptoms. The diagnosis depends on the demonstration of both gout and allergy. The three characteristics of gout, excess uric acid, deposition of crystals of sodium urate and recurrent attacks of acute arthritis, occur, but in allergy-gout the actual deposition of sodium urate is rare.

[This long, rather verbose article was based largely on experiences of the author and members of his family. The data seemed unconvincing to us.—Ed.]

Laboratory Data: 1. Relation of Blood Uric Acid to Gout. All methods of determining the uric acid content of blood depend on some modification of Folin's colorimetric methods; they all possess certain fundamental errors, according to Brøchner-Mortensen⁹⁹ who described his own method, based on the reduction of potassium ferricyanide. [Methods involving the use of this reagent have been considered inaccurate by some physicians.—Ed.] Determinations were made on serum. Brøchner-Mortensen's method gave the following results for 32 normal persons: for males, 5.4 to 8.8 mg. per cent; for females, 4.4 to 8.1 mg. per cent. When normal individuals were taking a purine-free diet, serum levels were about 1 mg. lower. There was no relation to age, stature and weight. The upper limit of normal (serum), therefore, was taken at 9 mg. per cent for males and 8 mg. per cent for females. Hyperuricemia was present in 22 (73 per cent) of 30 cases of gout. The degree of hyperuricemia was somewhat dependent on the length of the disease. During the first two or three years increased values were infrequent but subsequently were almost constant. No constant relation was observed between acute attacks and variations in the uric acid content of the serum.

[Readers are referred also to Brøchner-Mortensen's monograph⁹⁸ on uric acid in blood and urine.—Ed.]

The same author studied the excretion of uric acid by the kidneys of 30 gouty patients: no interference with clearance of uric acid as contrasted with that of urea and of creatinine could be demonstrated; three patients had nephrosclerosis; two chronic hemorrhagic nephritis and three, slight reduction of renal function. No difference was observed in the excretion of uric acid by normal persons and gouty patients after administration of purine.

2. Serum Protein. These were slightly low in four cases of gout.⁶⁷¹

[It was not stated whether the tests were done during or between attacks.—Ed.]

3. Sedimentation Rate. The sedimentation rate of erythrocytes was normal in 11 of the 30 cases of Brøchner-Mortensen, moderately increased [presumably during acute attacks—Ed.] in four and greatly increased in 15. With exceptions the rate was more or less proportional to the severity of attacks, but not with the level of blood uric acid.³¹⁰

4. Liver Function. Various tests of liver function revealed slight insufficiency in 14 of the 30 cases of Brøchner-Mortensen. This was attributed to associated alcoholism.

Etiology. An attempt was made by Grabfield³²² to associate gouty attacks with interference of the function of renal nerves. He noted that

cinchophen increases the excretion of uric acid of intact animals but not of animals with denervated kidneys. Ergotamine in appropriate doses blocks the sympathetic impulses to the kidney. When given in a case of gout, ergotamine produced a mild attack of gouty arthritis with diuresis of chlorides and reduction in excretion of uric acid. Thus interference with impulses through renal nerves produces effects similar to those observed in gout.

[Further studies along this line will be awaited with interest.—Ed.]

Levinthal suggested that the explosive onset of classical acute gouty arthritis may be caused by an exogenous antigen which only enters the circulation occasionally, or is absorbed through a breach in intestinal epithelium before the complete cleavage and denaturation of the food antigen [no proof given—Ed.].

Treatment. Conventional treatment was reviewed.^{128, 390, 449, 539, 789} The low purine, low fat, high carbohydrate diet advocated by Lockie and Hubbard (1935) was reported on favorably by Bartels. [As cinchophen was given simultaneously, it is impossible to evaluate the results.—Ed.] Massive doses of synthetic crystalline vitamin B₁ (as given by Vorhaus and Kramer) were used in nine cases by Callahan and Ingham. [As these patients received conventional treatment in addition, no conclusions can be drawn.—Ed.] Colchicine gave marked relief in Lockie's 75 cases of proved gouty arthritis but had no comparable effect in 50 cases of other forms of arthritis.

Action of Colchicine. The physiologic effects of colchicine on animal tissues were studied.^{41, 121, 140, 280, 346, 371, 581, 767, 768} Its effect on gout was unexplained. Colchicine increases mitotic figures: there is doubt whether it arrests cell division in the metaphase or whether it actually stimulates mitosis.⁵⁸¹

CINCHOPHEN TOXICITY

Toxic reactions from cinchophen in cases of gout or atrophic arthritis were not reported, but a patient of Coventry took cinchophen and anacin for "rheumatic fever," and nonfatal agranulocytosis (leukocytes 2600) developed.

The relationship of skin sensitivity to cinchophen toxicity was studied (Rawls, Gruskin, Ressa and Gordon). Cinchophen dissolved in blood serum was used for skin tests. In 30 of 50 cases "cinchophen toxicity" developed when 7½ grains were given three times daily for four weeks. Skin reactions were positive in 58 per cent of the entire group. Toxic reactions developed in 79 per cent of the cases in which skin reactions were positive, in only 33 per cent in which they were negative. Liver function tests gave normal results in 71 per cent of the cases in which reactions to skin tests were negative, in only 27 per cent in which they were positive. The authors concluded that such tests were of value in determining the likelihood of toxic reactions to cinchophen. [The list of symptoms used as evidence of "cinchophen toxicity" was pretty inclusive. Some patients with atrophic arthritis have some of these symptoms without having taken cinchophen.—Ed.] Winters, Peters and Crook noted that if pectin was fed to dogs that had peptic ulcers from cinchophen, healing occurred rapidly; if pectin was given concurrently with cinchophen, ulcers developed in only 11 per cent of the dogs,

whereas they developed in 100 per cent from cinchophen alone. Pregnancy and antuitrin S have little or no effect on cinchophen ulcers in dogs.²⁶⁴

[Peptic ulcer caused by cinchophen has not been reported in cases of gout.—Ed.]

THE URIC ACID PROBLEM

A method for estimating the "true uric acid concentration" of blood by means of uricase was described (Blauch and Koch⁸²). Fifty samples of human blood gave an average reading of 3 mg. per cent of uric acid by old methods and only 2 mg. by the "uricase method." Approximately a third of the color produced was considered due to substances other than uric acid. The uric acid content of certain mammalian bloods was estimated by this method.⁸¹ Since human blood does not destroy uric acid, it apparently contains no uricase. [This method should be tried in cases of unexplained high concentration of blood uric acid and in cases of gout.—Ed.] It was reported again¹⁰ that high fat diets reduce the excretion of uric acid of normal individuals. Grabfield found that sorbitol, mannitol, sucrose, raffinose and fructose, given intravenously, strikingly increased the urinary uric acid of dogs; dextrose, xylose, maltose and galactose did not produce a measurable increase. This effect was believed to be due to the alcoholic grouping at both ends of the chain. The use of some such substance to increase the uric acid output in gout was suggested. Grabfield and Swanson noted the effect of cinchophen on excretion of uric acid in normal dogs and in dogs with unilateral denervation of the kidney. Ureters of the dogs were first exteriorized. Cinchophen decreased the volume of urine both from the normal, and from the denervated kidney. It also caused a marked increase in excretion of uric acid from both normal kidneys in dogs used as controls. After denervation of one kidney cinchophen no longer increased the excretion of uric acid from either kidney. Thus, unilateral denervation produced effects similar to bilateral denervation. The coincident administration of ergotamine and cinchophen acted like denervation.³³²

The administration of purines augments uric acid clearance by at least 50 per cent.⁹⁹ Labor of pregnancy can produce a marked increase in plasma uric acid and the longer the labor the greater the increase.²⁰² One normal woman had a concentration of 10.4 mg. per cent of blood uric acid during labor. This returned to normal in a few days. According to Cadden and Stander, the increased blood uric acid in eclampsia is not due to decreased excretion but to impaired destruction of uric acid in the liver: five cases of eclampsia were studied: in all excretion of uric acid was normal. A review of the literature on urinary lithiasis with specific reference to uric acid stones was published.⁶²²

PSORIATIC ARTHRITIS

Incidence. The differentiation between true psoriatic arthritis and psoriasis with coexisting arthritis is often difficult. Arthritis of some sort appeared at some time or other during psoriasis in 25 per cent of Madden's

44 cases, in 8 per cent of Tobias' cases. The reported incidence of "psoriatic arthritis" varies from 1 to 7 per cent of cases of psoriasis.²⁵⁸ But many such cases do not represent true psoriatic arthritis; the incidence of the latter is more nearly 1 per cent of patients with cutaneous psoriasis, according to Epstein. Of Madden's 11 cases of psoriasis and arthritis, the arthritis did not immediately precede, accompany or follow the psoriasis in any case, but in one case there were simultaneous exacerbations and remissions of both the psoriasis and the arthritis. [Probably most of these were not cases of "true" psoriatic arthritis.—Ed.] About 200 cases of psoriatic arthritis have been reported in the literature.²⁵⁸

Definition. Psoriatic arthritis was defined by Epstein as "a form of atrophic arthritis associated with psoriasis and exhibiting a *reasonable amount* of synchronous activity, as evidenced by remissions and relapses, in the articular and cutaneous manifestations." Tobias considered the common type one with "primary involvement of the terminal phalanges."

Clinical Features. Details of 33 "typical cases" were given by Epstein, who differentiated the disease from keratosis blennorrhagica.

[Since Epstein did not see these cases but merely collected them from the literature his study is somewhat lacking in authority since he had to rely on the questionable diagnostic accuracy of others.—Ed.]

Fifty-two per cent of the patients were females. The disease may occur at any age but the greatest incidence occurred between the ages of 20 and 40 years. A mother and her daughter both had the disease. Reputedly heredity plays a rôle in 25 per cent of cases. In 18 per cent psoriatic arthritis and pustular psoriasis coexisted. The skin lesion generally appeared (average 6.6 years) long before joints became involved. When joints are affected, the skin lesion has generally become generalized; it was generalized in 79 per cent of these 33 cases. Joints were affected in the following percentage of the cases: hands in 97, knees in 69, feet in 61, ankles in 44, elbows and wrists each in 39, shoulders in 30, hips and "spine" each in 15, and sacro-iliac joints in three. The arthritis is basically of the atrophic variety, tends to be chronic and deforming, and may cause ankylosis. Small joints of hands are generally affected first, larger joints later. Patients with psoriatic arthritis are usually ambulatory except during acute relapses. Involvement of large joints may later confine the patient to bed; ankylosis of knees, ankles and other large joints may cause crippling. Nails of fingers or toes were affected in 79 per cent of the 33 cases. Pitting, longitudinal or crosswise ridging, and heaping up of amorphous material beneath nails were characteristic. The disease of joints and skin persists through life with frequent relapses and remissions.

Etiology. Psoriasis is believed by some to result from a disturbed fat metabolism and to be associated often with hypercholesterolemia. According to some, relapses in joints are associated with hyolipemia (Weissenback, Martineau and Bowens, 1938). But hypercholesteremia was usually absent in Madden's cases of psoriasis, and cholesterol tolerance tests were of no value in forecasting results of low fat diets.

Data on Psoriasis. Among Madden's 44 cases of psoriasis, remissions were ascribed to pregnancy, rheumatic fever and arsenic pills; exacerbations

to many factors including cholelithiasis. Thirty pregnancies affected eight psoriatic patients: in 14 pregnancies "the psoriasis almost disappeared"; lesions usually began to disappear at the end of the first trimester and the disease steadily improved during the rest of pregnancy. Whatever the effect of the first pregnancy on the psoriasis, succeeding pregnancies produced a similar effect.

[The effect of pregnancy on the arthritis was not stated.—Ed.]

Treatment. The effects of fever therapy ²⁵⁸ and of salts of manganese ⁷⁵⁷ on joints were "disappointing." Treatments for the skin lesions were reviewed. ^{298, 770} Of Madden's 22 patients given low fat diets (20 gm. daily), 68 per cent noted improvement in the skin lesions, but results may have been due to a general realinement of metabolism and tissue function rather than to correction of disturbed fat metabolism. The use of lipocaic (a neutral, alcoholic, fat free extract of pancreas) improved four of six patients with psoriasis. ⁷³⁰

HEMOPHILIC ARTHRITIS

In current papers on hemophilia joint changes were considered in only one: Newcomer presented a partial review of the literature and reported the clinical and radiologic features of hemophilic arthritis. In about 80 per cent or more of cases of hemophilia joint symptoms develop sooner or later for which operation is often mistakenly instituted. Intra-articular hemorrhage occurs and may cause destruction of cartilage. Degenerative joint changes and destruction of cartilage produce a "typical hypertrophic joint." Occasionally the changes are more atrophic than hypertrophic in type. Treatment of hemophilia with newer substances was described. ^{270, 400}

ALLERGIC ARTHRITIS

The small number of articles which appeared under this heading is a hopeful sign that internists and rheumatologists are becoming more critical. Only 2 articles dealing specifically with the subject appeared. Boemer presented nine cases of a triad, infection, arthritis, allergy, as a clinical entity. [The evidence was rather unconvincing.—Ed.] Wooton in a speculative mood, attempted to analyze food reactions of persons with "hypersensitive synovia." The method of determining sensitivity was not described and no controls were included. A case of "intermittent hydrarthrosis with an allergic basis" was described by Berger ⁶⁶ (see section on Intermittent hydrarthrosis). The relation of allergy to certain cases of gout was discussed by McKay (see section on Gout).

METABOLIC ARTHRITIS

This term, like allergic arthritis, is falling into disuse. No articles under this title appeared. A case of ochronosis was described by Bhatia (see section on Miscellaneous diseases of joints).

ENDOCRINE ARTHRITIS

Thyroid Dysfunction and Chronic Rheumatism. Some writers have blamed thyroid deficiency; others have cited thyrotoxicosis as the cause of certain cases of chronic arthritis. According to Crotti muscular and joint pains commonly develop in cases of hyperthyroidism. These are relieved by thyroidectomy but, if unrelieved, may lead to atrophic polyarthritis with contractures and general decalcification. Hyperthyroidism stimulates the parathyroids to overactivity with resultant demineralization.

[The evidence presented was unconvincing; there is still no proof that any endocrine abnormality alone can cause arthritis, but it may be an important contributing factor.—Ed.]

Menopausal Rheumatism. Our last Review discussed the rather vague concept of "menopausal rheumatism." Voight was the current sponsor of the idea that the menopause can not only produce "general rheumatic symptoms" but can affect unfavorably the course of "arthritis deformans." In a hypothetical manner Voight blamed "allergy of the climacterium" as the cause of various articular and muscular symptoms including the painful shoulder syndrome (peri-arthritis humeroscapularis) of typists, pianists and teachers undergoing the menopause. Cases of "menopausal arthralgia" and "climacteric arthritis" were described briefly by Ishmael and Howitt, but most American physicians doubt the existence of such entities.⁷⁵⁷

Joints and Parathyroids. Symptoms of hyperparathyroidism include pains in bones and joints, especially of lower extremities and spine, but true arthritis is not present. Features of the condition were reviewed.^{22, 24, 146, 352, 422, 467, 534, 682}

The disease may be present mildly for some time before producing characteristic chemical and roentgenologic signs.³⁵² Some⁵⁶⁸ regard scleroderma as a manifestation of hyperparathyroidism. [We do not.—Ed.] A "functional hyperparathyroidism" may occur in cases of hyperthyroidism according to Crotti. [One of us, W. B., has been unable to demonstrate this.—Ed.] In such cases muscle and joint pains and even a true "thyrotoxic chronic arthritis" may be present. In Sharpe's case of hyperparathyroidism multiple "rheumatic pains" were present. In the first case of Anspach and Clifton the child complained of pains in bones of extremities, in back and fingers, and a knee was enlarged; roentgenograms revealed epiphyseal enlargement, calcifications in tendons of knee and near an acromion bursa.

For patients who cannot or will not accept surgical treatment, roentgen therapy over parathyroids was recommended by some,^{24, 352, 422, 534} but not by others.⁴⁶⁷

[We consider roentgen therapy useless.—Ed.]

MISCELLANEOUS DISEASES OF JOINTS

Intermittent Hydrarthrosis. According to Berger⁶⁶ intermittent hydrarthrosis is not one disease but a manifestation of several general and

local conditions (malaria, rheumatic fever, undulant fever, lymphogranuloma venereum and other infections) [also atrophic arthritis if one is considering "symptomatic" and not "true intermittent hydrarthrosis"—Ed.]. To date 106 cases have been reported. The condition occurs with equal frequency in males and females, generally aged 20 to 45 years, and is sometimes familial. Contributory causes have been infection, endocrine disease and allergy. Some cases occur with menstruation and disappear at the menopause; pregnancy often holds attacks in abeyance. Each cycle is the same for a given person, usually eight to 13 days. Berger discussed the supposed value of endocrine products, ergotamine, vaccines, irradiation and surgical measures. In his case the condition stopped when foods to which the patient was sensitive were eliminated from the diet. These were lamb, apples, pineapples, grapefruit, peaches, tomatoes, string beans, corn, olives and grape jelly.

Synovitis. Irish and Stump reported a condition not sufficiently recognized. Improper distribution of weight due to weak feet causes villous synovitis of knees with hypertrophy and fibrosis of synovial villi and hypertrophy of subcutaneous soft tissues about the knee joint. "Correction of weak feet results in complete relief of subjective symptoms."

[We are not convinced that such an entity exists.—Ed.]

Tumors of Synovia and Joint Tissues. 1. *Synovial Sarcomas.* A case of popliteal synovioma was reported.¹⁴⁷ Our knowledge of malignant synovial tumors is scant for three reasons: (1) lack of knowledge of the nature of normal synovia; (2) rarity of cases of synovial sarcomas; (3) lack of precision in case reports. Berger⁶⁷ reviewed the entire literature and added five cases, four of which seemed to represent a distinct oncologic entity. In three cases the tumors were histologically similar, and originated in serous bursae; all recurred a few months after their surgical removal. In two cases pulmonary metastasis caused death. Proposing a new classification, Berger recognized three main types of tumors: (1) a type corresponding to benign xanthomatous giant cell tumors; (2) epithelioid sarcomatous tumors; (3) polymorphous tumors. The prognosis is bad. Treatment should be prompt and radical.

2. *Xanthomatous Tumors of Joints.* De Santo and Wilson reviewed the 32 reported cases and added nine new ones. Data on the 41 cases were tabulated.

Xanthomas are commoner than supposed; a preoperative diagnosis has apparently never been made. Obscure, intermittent swelling, pain and hydrops of a knee, occasional locking and a movable tumor, usually medial to the patella, may be caused by xanthoma. Aspiration of dark or sanguineous fluid suggests xanthoma, and demonstration of large amounts of cholesterol is probably pathognomonic. The tumors originate in chronic, hemorrhagic, villous arthritis. The stroma cell is related to the reticulo-endothelial system and produces three types of cells: (1) foam cell, (2) giant cell, and (3) pigmented cell. De Santo and Wilson viewed the condition as related to some disturbance of lipid metabolism. Radical excision was recommended. No malignant transformation was observed.

[Berger observed such a transformation in one case.—Ed.]

3. *Hemangioma of Joints.* Bennett and Cobey surveyed the literature on hemangiomas of joints and added five cases. Criteria for diagnosis and treatment were discussed. Difficulties inherent in surgical excision due to hemorrhage, and the unsatisfactory results in all save the small, pedunculated type of tumor caused the authors to institute therapy with radium (in one case) and roentgen-rays (in two cases) successfully, the first application of such therapy for this disease.

Arthritis with Coccidiosis. For a discussion of the study of Faber and his associates on the acute arthritis which may accompany coccidiosis see *Erythema nodosum*.

Pelvic Osteo-Arthropathy of Pregnancy. Excessive relaxation of pelvic joints during pregnancy may produce chronic backache and locomotor disturbances. Young recognized two types of trouble, involvement of (1) sacro-iliac joints alone, and (2) sacro-iliac and pubic joints. Pain occurs in these regions during pregnancy and is aggravated by walking; walking may be difficult or impossible; the gait may be waddling. Among 34 of 4512 pregnant women, these conditions developed.

Tenosynovitis. Many physicians are unfamiliar with de Quervain's disease—stenosing tenosynovitis or tendovaginitis of the tendons of the extensor pollicis brevis and the abductor pollicis longus. These tendons pass in a common sheath through a groove on the most lateral portion of the radial styloid process. Similar lesions may occur in the tendons of the flexor pollicis longus, extensor carpi ulnaris and flexor carpi radialis. [Would it not be better to discard the term "de Quervain's disease," and describe these conditions as stenosing tenosynovitis of the particular tendon affected?—Ed.] Reported were five cases by Diack and Trommald and one by McDonald and Stuart. About 70 per cent of such patients respond to conservative therapy, "immobilization of wrist and abducted thumb in plaster for six weeks." Simple incision of the sheath is almost always satisfactory.

Osteochondritis. The association of chondritis with internal derangement of the knee was discussed.²¹⁶ Osteochondritis of ankle (two cases),¹²⁴ knee (one case)¹²⁴ and elbow joint (one case)⁵⁵² was described. Freund discussed the relationship between osteochondritis dissecans of the head of the femur and partial idiopathic aseptic necrosis of the femoral head. Four cases of osteochondrosis deformans of the tibia were described.⁴⁴

Charcot's (Tabetic) Arthropathy. This was discussed under Syphilis of joints.

Pulmonary Osteo-Arthropathy. A case of pulmonary osteo-arthropathy secondary to carcinoma of the thymus was noted (Miller). In another case no primary disease was demonstrated although the patient had hypercalcemia.³⁹¹

Sclerodactylia and Scleroderma. The theory that dermatomyositis and symmetrical scleroderma with sclerodactylia are identical was advanced by Dowling and Griffiths who reported the pathologic findings from biopsy in

two cases, and stated their belief that the muscle changes are degenerative, not inflammatory. Ochsner and De Bakey considered scleroderma related to hyperparathyroidism.

Protrusio Acetabuli ("Otto Pelvis"). An exhaustive, profusely illustrated discussion of acetabular deformities was presented by Gilmour who distinguished primary from secondary protrusions. The former are related to development of the bony pelvis, are commonly bilateral and preponderate in females. The latter are due to destructive disease of the hip or to trauma, and are usually unilateral. Twelve case reports were presented and the clinical features of 41 cases were reviewed.

Cutis Elastica (*Dermatorrhexis*, *Ehlers-Danlos Syndrome*). Cases were reported by Smith⁷⁰³ and Burrows and Turnbull but nothing new was added to that noted in previous Reviews.

Congenital Anomalies: 1. Amyoplasia Congenita. Multiple congenital articular rigidity (myodystrophia foetale deformans, arthrogryposis multiplex congenita) is a symptom complex which includes congenital, symmetrical, joint rigidities of various degrees without inflammatory changes. It is believed to be an aplasia. A case was described.¹⁷

2. Discoid Cartilage (Trigger Knee). This condition represents a persistence of the embryonic external semilunar cartilage. Three cases in which surgical treatment was used were described.⁵⁶⁷ The comparative anatomy of the knee joint in relation to congenital anomalies was discussed.⁶⁷⁰

Ochronosis. A typical case of alkaptonuria with ochronosis was described by Bhatia. The patient had been bedridden for 10 years because of vague pains all over the body and arthritis of the knees and interphalangeal joints. Present were purpuric rashes for which there was no explanation other than the ochronosis.

DISEASES OF BURSAE

General Comment. A good synopsis of the anatomic and etiologic types of bursitis was given by Ghormley who discussed treatment of the various types including "housemaid's knee" (prepatellar bursitis), "miner's elbow" (olecranon bursitis), and "Albert's disease" (retrocalcaneal or deep Achilles bursitis). Infection, trauma and metabolic disturbances (e.g., gout) are chief causes. The pathologic reaction varies with the cause and stage of the process. An important complication is intrabursal calcification which develops "when sufficient fibrosis exists, when the hydrogen ion concentration is ideal and when the blood supply is inadequate."^{76, 307} Treatment depends on the nature and severity of the bursitis, and varies from surgical procedures such as incision, excision or needling to conservative measures such as rest, heat, roentgen therapy.^{307, 308}

Current writers^{76, 114, 141, 548} considered trauma a more important cause of bursitis than infection. A common sequence of events is trauma to the bursa or to tendons adjacent to the bursa, partial rupture of a tendon already

somewhat degenerated by age, the development of inflammation, adhesions and calcium infiltration of the *tendon* with *secondary* irritation or inflammation of the bursa, and spasm and contractures of adjacent muscles. For this reason it is not entirely correct to speak of, e.g., "subacromial bursitis" because other structures besides the bursa are primarily or secondarily affected.

Special Types of Bursitis. "Tennis elbow" was discussed briefly.^{193, 307, 315} Conservative measures (rest, perhaps splinting, heat, massage) are preferred to surgical excision.

Inflammation in the bicipitoradial and interosseous bursae of the elbow may cause nontraumatic paralysis of the dorsal interosseous nerve with progressive paralysis and atrophy of phalangeal extensors, according to Weinberger.

Cases of metacarpophalangeal or interphalangeal bursitis were reported.^{188, 381, 406} An operation for Achilles bursitis was described.⁸³¹

DISEASES ABOUT THE SHOULDER JOINT: THE PAINFUL SHOULDER

"Subdeltoid or Subacromial Bursitis." This is more than a bursitis; indeed in some cases bursal involvement is either absent or of minor importance. Writers again stressed the fact that the primary lesion is generally a partial or complete rupture of the supraspinatus tendon near its insertion, with subsequent inflammation therein and in adjacent tissues, leading to adhesions and disability of the abductor and rotator muscles of the shoulder girdle.^{8, 76, 141, 309, 548} The various symptoms produced by these lesions and the differentiation between partial and complete ruptures were described in detail (as in previous Reviews).^{8, 114, 141, 313, 548, 634, 716, 830} In some cases symptoms resemble those of "brachial neuritis" or the "scalenus anticus syndrome" (pains in neck muscles, scapular region and sometimes down the arm to finger tips).⁷⁶

Treatment. For acute cases rest, heat and narcotics were generally advised, but the shoulder should be rested in abduction, not adduction.^{193, 195, 197, 203, 634} Short wave therapy,¹¹³ conventional diathermy,⁷⁶⁹ fever therapy¹⁰² and roentgen therapy³⁸¹ were recommended. Instead of rest, Moseley advocated daily motion, from the onset of treatment, made possible by using injections of novocaine and diathermy. In acute cases (with or without calcium deposits) unrelieved by these measures, several physicians strongly recommended needling and lavage with saline and novocaine.^{76, 141, 634, 729, 830} Relief is often prompt and complete. Others^{114, 313, 716} favored early surgical repair in cases of partial, as well as of complete, rupture of the supraspinatus.³⁹⁹ Horwitz³⁹⁹ recommended operation only for patients under 40 years of age.

For more chronic cases intensive physical therapy, curettage of calcium deposits⁶³⁴ or manipulation with^{141, 525, 634, 784} or without⁸ anesthesia was advised. Roentgen therapy was favored by others^{75, 188, 505, 830} as a "com-

paratively specific" means for relieving pain and fostering absorption of calcium deposits. On the theory that "allergy of the climacterium" caused painful stiff shoulders, Voight used large doses of progynon and local histidine iontophoresis; restitution of normal motion was claimed [no statistics given—Ed.].

Pain about shoulders may be caused by lesions other than in the supraspinatus tendon, among them fibrositis of adjacent muscles, cervical hypertrophic arthritis, and contracted, hypertrophied or anomalous scalenus anticus muscle.^{8, 313, 407, 472, 716}

Peritendinitis Calcarea. Bursitis calcarea is probably a manifestation of this condition which affects hips and knees as well as shoulders; calcium deposits often rapidly disappear after roentgen therapy according to Copland and Michel.

[Such deposits often disappear rapidly spontaneously.—Ed.]

DISEASES OF MUSCLES AND FIBROUS TISSUE

A clinical pathologic study of muscular diseases was made by Geschickter and Masseritz who classified their cases of myositis as follows:

	Cases
Acute:	
Nonspecific, abscess formation	6
Nonspecific, no abscess formation	2
Chronic:	
Nonspecific, abscess formation	2
Nonspecific, no abscess formation	17
Tuberculosis	15
Syphilis	8
Trichinosis	6
Torticollis	17
Volkman's ischemia	7
Myositis ossificans	25
Diphtheria	1
Progressive muscular dystrophy	2

They emphasized the difficulties of diagnosis in the chronic group, and, in view of their frequency, urged that tuberculosis, syphilis, trichinosis and the exanthematous diseases be considered, and biopsy be done if diagnosis is obscure. Two cases of trichinosis were noted in which findings suggested the presence of arthritis without clinical symptoms of trichinosis. Diagnosis was made by biopsy. A classification of muscle tumors was also given.

DISEASES OF MUSCLES CAUSED BY TRAUMA

Rupture of Muscles. Symptoms due to partial or complete rupture of various muscles were described and treatment was outlined.³¹³

Myositis Ossificans. Eleven cases of this disease following injury were reported by Hirsch and Morgan. A bony mass was removed surgically in all cases. Cartilage and fibrocartilage were found in varying degrees of differentiation. Fibrocartilage is a normal constituent of the insertions of many tendons in which traumatic ossification occurs. Reactive or repara-

tive growth of these tissues initiated by trauma provides a simple explanation for the traumatic ossification. Complete immobilization of the involved region was Kleinberg's⁴⁵⁸ early treatment of choice.

Ossification of the anterior cruciate ligament following injury was described.³⁰⁰

FIBROSITIS

Fibrositis accounts for from 30 to 60 per cent of all cases of rheumatic diseases according to some physicians.⁷ [Two of us, W. B., and M. H. D., do not agree; we believe that the term "fibrositis" is too loosely used and that many cases of "fibrositis" represent other conditions.—Ed.] About 75 per cent of the cases encountered at the arthritis clinic, De Paul Hospital, St. Louis in 1938 were of fibrositis. It is surprising therefore that of all the articles under review only three were concerned chiefly or solely with fibrositis.^{7, 210, 555} Fibrositis was classified by Abel, Siebert and Earp thus: (1) primary fibrositis; an affection of fibrous tissue independent of atrophic arthritis or any other articular disease; in these cases atrophic arthritis practically never develops later; (2) secondary fibrositis; fibrous tissue changes secondary to atrophic arthritis, specific infections, trauma, etc.; (3) senile fibrositis; fibrositic changes which occur with age. Of their 71 cases these writers called 55 primary and 16 secondary (20 acute and 51 chronic).

[It is not clear whether they listed their cases of senile fibrositis as primary or secondary.—Ed.]

Symptoms. These were described^{7, 555}; morning stiffness of muscles and joints, "jelling" after rest, general exhaustion which is usually worse as the day wears on, moderate relief from moderate exercise, exacerbations from overexertion. Symptoms of fibrositis of muscles of the neck and fibrous tissues of the scalp which produce "rheumatic headaches" (first described in 1615) were discussed by Cyriax.

Pathology. In an unstated number of cases Abel, Siebert and Earp made muscular biopsies. In the acute and subacute cases hemorrhages, hyperemia, serofibrinous exudate between the muscle bundles, newly formed fibroblasts, mild degenerative changes in the muscle, swelling and loss of cross striation and a few inflammatory cells, chiefly lymphocytes were found. In the chronic cases fibrosis of muscle fascia and intramuscular septa with separation of muscle bundles, marked degenerative changes in muscles including complete loss of cross striation, hyalinization, and fat between muscle bundles were present. [Then why isn't this "myositis," not "fibrositis"?—Ed.] At necropsy of patients with osteo-arthritis who had complained of backache, sections of muscles showed definite fibrositis. For others with equal or greater changes from osteo-arthritis who had not complained of backache there was no associated fibrositis of the muscles.

[Unfortunately the authors summarized these findings too briefly for them to be of much value. No case reports were given with related data on pathology. The pathologic findings were classified as acute or chronic, but it was not stated when

they were from cases of primary or secondary fibrositis. It is difficult to believe that the muscular lesions of primary fibrositis (no muscle atrophy or notable flexions) are identical with those of fibrositis secondary to atrophic arthritis.—Ed.]

Etiology. The relation of fibrositis to infected foci was considered doubtful by Abel, Siebert and Earp: "The pathologic findings in our cases correspond more with an allergic response than an infection." [But the pathologic reactions described above do not conform to those of orthodox allergy.—Ed.] According to Levinthal "fibrositis" (type not stated) may represent an anaphylactic reaction to several unknown antigens but seems to be related to streptococcal infections in 25 per cent of cases [no proof—Ed.]. Chilling, respiratory infections and influenza are common precipitating factors. According to Pennington fibrositis is only the pathologic expression of a normal physiologic fatigue process related to an inefficient mechanism in both skin and lymphatic drainage of, possibly, lactic acid; the development of better chemical methods for analyzing sweat may permit one to prove this idea. Rosenow noted 64 cases of fibromyositis associated with encephalomeningoradiculitis, the result of epidemics of poliomyelitis, 1934 to 1936. Symptoms were multiple and included pains in back, extremities, heels, and wrists and in several cases fibrous ankylosis of interphalangeal joints preventing fist-clenching. Extensive bacteriologic studies were made on a streptococcus isolated from foci. Shorbe noted nine mildly febrile cases of lumbar myofasciitis possibly due to brucellosis.

Treatment. Conventional treatment was outlined^{7, 33, 555}; removal of infected foci, use of physical therapy, especially massage, use of warm clothing; avoidance of chilling, drafts, colds and influenza. No special diet was generally advocated, but Bach³³ prescribed a lactovegetarian diet in cases presumably caused by intestinal putrefaction. [He did not say how this could be proved or satisfactorily presumed.—Ed.] Neligan and Cyriax upheld the English view on the great value of heavy massage: in cases of "rheumatic headaches, provided the correct spots are massaged firmly and persistently, there should be next to no failures." According to Crichton-Miller patients whose fibrositis fails to respond to physical therapy may have some psychologic reason for wishing to remain ill or to continue treatments; some of the motives were discussed. Others⁷ considered heavy massage provocative of exacerbations, and used light massage only, and that only in chronic cases. In acute cases moist heat is preferable to diathermy.^{105, 107} Recommended were autohemotherapy and/or fever therapy,⁴²¹ bee venom,¹² streptococcal vaccine,⁸⁰³ Crowe's vaccine⁷ and colloidal sulfur.²⁸² For lumbar fasciitis Creer and Romer recommended early manipulation under anesthesia as productive of much quicker results than those from rest, heat, etc.: it may give "instantaneous relief." [The technic was not given nor the reason why such therapy should give results.—Ed.] Injections of procaine were strongly recommended by Steinbrocker for lumbar fasciitis, by Cyriax for cervical fibrositis. For diffuse lumbar or gluteal fibrositis Steinbrocker made deep injections of 10 c.c. of 2 per cent procaine with 25 to 100 c.c. normal saline

solution. Painful tender nodules were penetrated with a needle; 5 to 10 drops were deposited therein and 3 to 5 c.c. injected around the nodule. For nodules unaffected thereby he injected 3 to 6 mm. of 95 per cent alcohol into the nodule, 5 c.c. aqueous procaine solution around the nodule. Of 15 patients with fibrositis so treated 10 obtained "marked or complete relief." Cyriax infiltrated persistently tender cervical spots in muscles with 1 in 200 watery solution of procaine or 1 in 50 solution of procaine in olive oil.

MISCELLANEOUS DISEASES OF MUSCLES

Dermatomyositis. Two cases of dermatomyositis with progressive scleroderma were reported by Dowling and Griffiths who consider dermatomyositis and progressive symmetrical scleroderma the same disease. Sheldon, Young and Dyke reported the clinical and pathologic findings in a case of acute dermatomyositis with a skin rash, attacks of edema in the leg muscles, and severe muscular weakness with fibrosis: at necropsy generalized reticulo-endotheliosis with localization in liver, spleen and mediastinum was found. It was suggested that dermatomyositis may represent a derangement of the reticulo-endothelial system. Because of profound weakness, malaise, gastrointestinal disturbance, loss of weight, pigmentation of skin and postural hypotension, a case of dermatomyositis and scleroderma, proved at necropsy, was first diagnosed as Addison's disease.⁷⁵¹ [Cases of pigmented scleroderma suggesting Addison's disease are not uncommon.—Ed.] Three cases of dermatomyositis among children were reported by Bruce; all had identical retinal lesions with extensive regions of whitish exudate and small hemorrhages. Other cases of dermatomyositis were reported.^{60, 142, 379, 445} A case of poikilodermatomyositis was reported by Guy, Grauer and Jacob in which there were all the features of dermatomyositis plus poikiloderma; they implied that the latter is a variant of the former.

Miscellaneous Conditions. Eighteen cases of *tropical pyomyositis* unrelieved by malaria and antisyphilitic treatment, responded dramatically to sulfapyridine.²⁴² Five cases of *epidemic myalgia* (devil's grip, pleurodynia) occurring in the same family were reported.⁴⁰⁴ Two cases of *myositis fibrosa* were reported.^{80, 712}

MISCELLANEOUS CONDITIONS

Periarthritis Nodosa. "Arthritis" and muscle pains, "polymyositis," may occur in this disease; hence rheumatologists should become familiar with it. Among the 11 cases reported this year diagnosis was unsuspected until postmortem examination in seven, was made by biopsy in two, and suspected antemortem in two others. Only eight cases of periarthritis nodosa have been recognized among 53,000 patients at Peter Bent Brigham Hospital.

Harris, Lynch and O'Hare reported six cases. The complete confusion in symptoms is best illustrated by briefing their six cases: Case 1: Chinese woman with sea-

sonal allergic rhinitis, chronic glomerulonephritis and cirrhosis of liver; death from uremia: widespread periarteritis nodosa at necropsy. Case 2: young Greek student with polyarthrititis, low grade fever, leukocytosis, splenomegaly and cutaneous nodules; periarteritis nodosa at biopsy; patient recovered and has been well four years. Case 3: a surgeon complaining of exhaustion, arthritis, fever, tachycardia, hypertension and anginal attacks; signs of glomerulonephritis; periarteritis nodosa clinically and at necropsy. Case 4: woman with hypertrophic arthritis, emphysema and chronic myocarditis; death from congestive heart failure and bronchopneumonia; periarteritis nodosa at necropsy. Case 5: man with fever, foot and wrist drop, and chronic glomerulonephritis; death from bronchopneumonia; clinical diagnosis, polyneuritis; periarteritis nodosa at necropsy. Case 6: fireman with gastric ulcer and hematuria; death from uremia; periarteritis nodosa and gastric carcinoma at necropsy.

Harris, Lynch and O'Hare, having studied all cases reported before 1938, concluded that there is no characteristic symptomatology. Of the 101 reported cases recovery occurred in 10. Males predominated 3 to 1. Ages were from 6 to 71 years; average was 36.9. "*Arthritis*" occurred in 27 per cent. [Its characteristics were not described.—Ed.] Common symptoms, in order of frequency, were fever, leukocytosis, albuminuria, abdominal pain, edema, loss of weight and hypertension. Most frequent organs involved were kidneys in 87 per cent, heart in 84 per cent, liver in 71 per cent, spleen in 31 per cent, lungs in 25 per cent.

One fatal case of periarteritis nodosa with livedo reticularis, was seen (Ketron and Bernstein). Other cases were reported^{143, 279, 610, 653, 805}: in one the first diagnosis was "arthritis."⁵⁴⁷ "The history of periarteritis nodosa disposes to clinical humility. All that can be said is that it is a freakish vascular disease of unknown origin likely to prove fatal in a few weeks or months, occasionally years, and producing extremely varied clinical manifestations with no known preventive nor any known cure" (Fitz, Parks and Branch).

Aseptic Bone Necrosis. Four cases of long standing caisson disease producing aseptic bone necrosis and "arthritis deformans" (i.e., hypertrophic arthritis) were reported by Kahlstrom, Burton and Phemister.

Bone necrosis was produced by injury of tissues from the release of nitrogen bubbles due to too rapid decompression. Uncertainty prevails as to whether the bone damage is due to the obstruction of end-artries by gas embolism or by direct pressure on blood vessels and other tissues after liberation from solution in the marrow fat. One case came to necropsy; in another biopsy was done on the involved femur. When necrotic bone was situated in the epiphyses and bordered on joints, varying amounts of collapse occurred. Articular cartilage overlying the involved parts had broken down and had been replaced by fibrocartilage; a more or less extensive arthritis deformans resulted. This supported the theory that arthritis deformans may be due to vascular blockage and necrosis of bone underlying articular cartilage. Attempts to produce bone lesions in dogs by air emboli were unsuccessful. In three cases with no history of caisson disease, Kahlstrom, Burton and Phemister noted almost identical findings as those found in caisson disease. [They were the first such cases reported.—Ed.] Roentgenograms revealed lesions similar to those just described for caisson disease, areas of massive infarction of bones with the development of arthritis.

Disseminated Lupus Erythematosus. This may produce symptoms resembling rheumatic fever, atrophic arthritis, or fibrositis.

A case with postmortem findings was reported by Contratto and Levine. Because of a prolonged P-R interval (0.24 sec.) and fever associated with joint pain and swelling, the initial diagnosis was rheumatic fever [a not unusual error.—Ed.]. The true diagnosis later became evident with the appearance of the cutaneous lesions. Roentgen therapy was given over the ovaries in an attempt to sterilize the patient. This was done because the authors had never seen this disease except in women between the onset of puberty and the beginning of the menopause. Temperature dropped rapidly after roentgen therapy; the patient felt much improved for two days, but lobar pneumonia developed and the patient died. Necropsy disclosed lupus erythematosus disseminatus but no evidence of rheumatic fever. The only pathologic feature now recognized as specific for this disease is the skin lesion.⁵⁴⁴ A classification with illustrative cases was given by Urbach and Thomas. Sulfanilamide seemed useful to some,⁷¹⁵ but not to others.⁸¹⁶

Variable Symptom Complex. A variable symptom complex of undetermined etiology with fatal termination was described by the Reifenshteins who added a case to 17 in the literature. Articular manifestations (usually polyarthritis) and pleuritis were present in each case. Synovial hypertrophy, subperiosteal bone formation and capsular edema have been noted. In most cases prolonged fever, polyserositis, erythematous cutaneous lesions, nephritis, anemia and a remittent cachectic course with fatal termination occurred. This variable group of symptoms has been called many different names (Libman-Sacks' disease, Pick's disease, lupus erythematosus, periarteritis nodosa, etc.). The cause is unknown. Such cases should be grouped for further study.

[Christian's case, 1935, was noted in our Third Review. The case of the Reifenshteins may well have been one of lupus erythematosus.—Ed.]

Multiple Myeloma. This may produce symptoms suggestive of atrophic arthritis as it did in the cases of Tarr and Ferris: nodular deposits of amyloid were in and about joints.

OTHER STUDIES ON JOINTS AND RELATED TISSUES

Articular Roentgenography. An improved technic for roentgenograms of knee joints was again⁶ described.³⁹² By using a better articular position clearer visualization of joint space, joint mice, loose bodies, etc., is obtained. "Pneumarthrography" was considered valuable in the diagnosis of athletic and industrial injuries.³⁶¹ Lindblom used a contrast medium soluble in water (perabrodil) for injection into knee joints without serious reactions. Crucial and tibial collateral ligaments were thus visualized.

Articular Physiology. After studying synovial sarcomas Berger⁶⁷ posed these questions: 1. Is the synovial membrane a simple endothelium, a modified cartilage, a reticulohistiocytic or a truly autonomous and specific tissue? 2. Is the synovial fluid the result of a direct or indirect secretion and what is the mechanism of mucin formation?

He concluded that synovial tissue has peculiar characters setting it apart as a variety *sui generis* of the reticulo-endothelial system. He proposed the designation "synoviothelial" for synovial tissue, as employed by Hueck and in accord with Vaubel's conception of synovioblasts. He concluded that mucinogenesis is entirely different from mucous secretion in glandular cells and may be comparable to the intercellular substances appearing in mesenchymatous tissues. Synovial fluid may be analogous to cartilaginous and osseous intercellular substances except that in synovial tissue the substance remains liquid.

The absorption of mecholyl from knee joints of cats was reported.⁶²⁶ Experiments were carried out on normal joints, joints mildly inflamed by saline injections, and joints experimentally inflamed by aleuronat. From all normal joints mecholyl was absorbed readily, more rapidly with exercise. Inflammation increased the rate of absorption both at rest and after exercise. Other experiments with adrenalin, pituitrin and pilocarpine led to the conclusion that absorption was largely by the blood stream, a very small amount being absorbed slowly through lymphatics. Bennett and Shaffer studied the transference of proteins from blood into knee joints of rabbits, also the passage of protein into aqueous humor, spinal fluid and urine. Crystalline egg albumin was transferred from the vascular system into the knee joint within five minutes. Amounts of egg albumin in joints tended to vary directly with that in serum. Egg albumin was also speedily removed from the joint and was excreted largely unchanged in urine. Similar results with isotonic solutions were reported.²⁷⁷ Meyer, Smyth and Dawson isolated from synovial fluid a mucopolysaccharide apparently similar to that in vitreous humor, umbilical cord, and also in group A hemolytic streptococci. Theories on the nature and origin of synovial fluid were reviewed by Ropes, Bennett and Bauer who analyzed synovial fluid from the astragalotibial joint of cows. They concluded that normal bovine synovial fluid is a dialysate of blood plasma. Unlike other dialysates synovial fluids contain mucin of unknown origin. Mucin plays a definite rôle in the exchange between blood capillaries and the joint space.

Burman and Kling studied the excretion of Evans' blue dye into synovial effusions of five patients with atrophic arthritis; amounts of the dye in effusions were directly proportional to the activity of the rheumatic process. Postmortem study of a case of spastic quadriplegia and athetosis permitted Freund to study joints, some long disused, others long overused. The study indicated that joint cartilage degenerates and is replaced by fibrous tissue if it lacks contact with its antagonist. The same changes occur if pressure is too great or if near normal pressure be maintained for too long a period continuously. "There is nothing specific to hypertrophic arthritis. Any marked alteration of function for a long period (infra- or ultra-physiologic demands) leads to degenerative changes of joint cartilage and may be followed by the whole syndrome of fully developed arthritis deformans."

The lateral parts of joint cartilage, according to Fisher,²⁷⁷ receive nourishment from the *circulus articuli vasculosus*; the central portion is less well

nourished by synovial fluid; hence there are differences in rate of repair of the central and lateral parts. An experimental injury to the central portion remains unhealed for a long time, then healing occurs largely by connective tissue formation. The same injury to the lateral portions heals more rapidly with true proliferation of cartilage. Removal of the central portion is followed by a compensatory proliferation of the lateral margins, thus forming a typical osteo-arthritis.

[One of us, J. A. K., believes that this marginal proliferation is not compensatory but due to the increased blood supply incident to repair of the defect.—Ed.]

Abercrombie discussed the influence of morphologic structure on the pathology of joints, the relation of the former to the frequency and location of fibrositis and arthritis in certain sites.

Articular Function. A new instrument for measuring joint motion was described.⁸¹³ Degrees of normal motion of all joints as measured by this method were tabulated. Montgomery discussed the knee from a historical and philosophic viewpoint.

Experimental Arthritis. 1. *Infectious.* A spontaneous polyarthritis in rats was studied by Findlay and associates who isolated from joints a pleuropneumonia-like organism which reproduced the disease when injected into pads of mice and rats. Other species of animals were unaffected. The experimental arthritis was dramatically affected by gold salts but not by sulfonamide compounds. Sabin produced a proliferative chronic polyarthritis resembling somewhat human atrophic arthritis by injecting mice with a filtrable pleuropneumonia-like organism isolated from the brain of a normal mouse. The experimental arthritis was produced almost constantly in 150 mice by one intravenous or intraperitoneal injection. It was migratory, chronic and progressive, often with fusiform swelling and ankylosis. No tissues but joints seemed affected; all the 150 mice appeared in good health; none died. A second strain of the organism produced a disease much more like rheumatic fever. [Sabin could not isolate such organisms from patients with rheumatic fever or with atrophic arthritis, but urged the application of such studies to human arthritis.—Ed.] Collier also observed a similar spontaneous polyarthritis in rats which he reproduced by injection of sterile joint material into pads of other rats; no organisms were isolated. Others⁶²⁷ reported similar findings.

[These studies of Collier, Sabin, Findlay and their colleagues have aroused much interest. Although Sabin was unable to do so, Swift and Brown reported the apparent recovery of pleuropneumonia-like organisms from cases of rheumatic fever, and erythema nodosum. But they subsequently found that the organisms in reality came from mice, not from the rheumatic patients. Despite this these studies are important because the polyarthritis in mice and rats strongly resembles human atrophic arthritis, and can be reproduced experimentally. Hence an important new type of arthritis is at hand for studies on experimental therapy. In this connection the studies of Dienes and Sullivan^{228, 738} are of interest.—Ed.]

Various types of streptococcal arthritis were produced experimentally. Rosenow again described his well known type of streptococcal (viridans)

arthritis. Iritis is a not uncommon complication of atrophic arthritis; hence Berens, Angevine, Guy and Rothbard carefully studied the eyes of rabbits in which experimental arthritis was induced. Ocular and articular inflammations were produced by various bacteria, especially by streptococci given intravenously. Organisms from patients with ocular disease produced more eye lesions in rabbits than strains from other sources. Animals with arthritis had no more eye lesions than animals with no arthritis; that is, no relationship was noted between involvement of eyes and joints. Infected foci were experimentally produced; few eye lesions resulted. Cecil, Angevine and Rothbard produced arthritis in rabbits by injecting into various sites, several strains of streptococci, usually hemolytic; arthritis was also produced by staphylococci and pneumococci. The disease was never migratory; joints were not affected symmetrically and those affected were not ones commonly involved in atrophic arthritis. Although the pathology of this experimental chronic arthritis was very similar to that found in atrophic arthritis, the authors did not conclude that they had produced the human type of disease; rather they concluded that the histopathology of atrophic arthritis is not specific. Gordon produced fibrositis and arthritis in rabbits by injecting a virus (*variola lapine*). Hemolytic streptococci injected with the virus produced a more marked arthritis than comparable doses of either alone. Observations on experimental type III pneumococcic arthritis were reported by Shaffer and Bennett.

2. *Chemical and Nutritional.* The Silberbergs studied further⁶ the effect of estrogen and anterior pituitary extract on development of bone and cartilage. In immature guinea-pigs gonadectomy caused an increased proliferation of euhyaline cartilage; hyperplasia was more pronounced in males and hypertrophy in females. Degenerative changes were more marked in males. In old animals given anterior pituitary hormone severe arthropathic changes comparable to those of human "arthritis deformans" were produced. Estrogen administered to immature guinea-pigs caused retrogressive changes, increased hyalinization and ossification indicating a premature aging of the cartilage. Previous experiments⁶ on the effects of potassium iodide on cartilage were repeated on animals after thyroidectomy. Proliferation of euhyaline cartilage still occurred as it did when operation was not performed. However, the increase in the number of hypertrophic cartilage cells, the decrease of ossification and the resorption of bone which occurred when operation was not performed did not appear in the animals following thyroidectomy. Nunnemacher reported studies on the cartilage plates of long bones in the rat.

Palcopathology. A note on the relationship between oral sepsis and arthritis in prehistoric times appeared.^{7,8}

Physiology of Muscles. Attempts were made by Maison to produce ischemic pain by injecting ammonium chloride, potassium chloride and sarcolactic acid into muscles: it was concluded that they are not responsible for

such pain. In a paper which cannot be reviewed adequately herein, Wright discussed the mechanism of pain, particularly that arising in muscle, the metabolism of skeletal muscle and the properties of muscle extracts, the interchange of fluid between blood and tissues, the flow of lymph, the rational basis of massage, and the effects of reactive hyperemia, heat and artificial fever.

Finding no changes of bones or joints in the hind limb of cats following complete denervation (lumbar sympathectomy and section of fourth lumbar to third sacral "dorsal roots"), Corbin and Hinsey concluded that bones and joints are not supplied with nerves having a specific trophic function.

CAMPAIGN AGAINST RHEUMATISM

The literature under review, written before the Blitzkrieg, showed no influence of the war on the campaign against rheumatism. [But letters received recently from British and other European sources indicate an almost total cessation of the campaign.—Ed.] Davidson repeated his plea for a British national campaign against rheumatic diseases, emphasizing the inadequacy of hospital facilities for British arthritics. This same difficulty exists in the United States, where most hospitals are financially and psychologically "geared" only for the care of acute illnesses and injuries and have little room for, and less interest in, cases of chronic arthritis. According to Fantus large city hospitals, such as the Cook County, can accept arthritics only for a short examination or brief period of treatment. Hospitals should meet their responsibilities more adequately and provide not only ample outpatient facilities for continued therapy, but also special units for research and hospital treatment. English physicians joined Davidson in his insistence that hospital and other facilities for rheumatic patients are so grossly inadequate in England that the most urgent need for effective action is in the political, rather than in the medical, field. "If all the money wasted on [advertised remedies] was applied to a fund it would be possible to establish a central clinic in each town."⁵⁹ The British advertisers' association has barred advertisements of remedies to "cure," "banish" or "conquer" chronic arthritis.²⁵⁴

"The treatment of chronic rheumatic diseases is the business of the Nation and can no longer be left entirely to voluntary effort. Like the treatment of tuberculosis it must be combated by government, county councils, boroughs and municipalities. The public must be educated to the need for 'a mass attack' on this scourge—for it is a scourge": such was Pringle's opinion. Smart sought changes in the British Insurance Act so that physicians could prescribe, with governmental aid, physical therapy, and not just pills, for arthritics. He also urged the establishment in England of more industrial clinics where patients with early traumatic or infectious rheumatism could get early and adequate treatment: much money would be saved for industry. The two Travelling Fellows of the Empire Rheumatism

Council, Tegner and Duthie, expressed complimentary opinions of American arthritis units visited by them and recommended the establishment in England of similar units.

Despite the imminence of war the Empire Rheumatism Council prosecuted its campaign with vigor, raised large sums of money for fostering rheumatism units and research, and established affiliations in various Dominions and Colonies. Their broad, excellent plan of action, heartily sponsored by the Duke of Gloucester, the Lord Mayor of London and others, was again described.^{257, 397} Despite the approach of war the British effort continued unabated. As the Duke of Gloucester²⁵⁷ said, "It is surely proof of the sober strength of mind of the British race that, despite circumstances of no little discouragement, we can give our attention to a campaign which aims to enlist our energies against the common enemy of human happiness—the forces of destructive disease. We have good cause to believe that the problem of rheumatic diseases will be solved by persevering effort." Unfortunately these brave words cannot now be implemented by action anywhere in Great Britain or Europe. Until peace returns the responsibility of continuing the campaign rests on the medical profession of the Americas. It is our belief that the campaign will be prosecuted here with increased vigor.

REFERENCES

1. *First Rheumatism Review*: HENCH, P. S., BAUER, WALTER, FLETCHER, A. A., GHRIST, DAVID, HALL, FRANCIS, and WHITE, PRESTON: The present status of the problem of "rheumatism"; a review of recent American and English literature on "rheumatism" and arthritis, ANN. INT. MED., 1935, viii, 1315-1374; 1495-1555; 1673-1697.
2. *Second Rheumatism Review*: HENCH, P. S., BAUER, WALTER, FLETCHER, A. A., GHRIST, DAVID, HALL, FRANCIS, and WHITE, T. P.: The present status of the problem of "rheumatism" and arthritis; review of American and English literature for 1934, ANN. INT. MED., 1936, ix, 883-982.
3. *Third Rheumatism Review*: HENCH, P. S., BAUER, WALTER, FLETCHER, A. A., GHRIST, DAVID, HALL, FRANCIS, and WHITE, T. P.: The problem of rheumatism and arthritis; review of American and English literature for 1935, ANN. INT. MED., 1936, x, 754-909.
4. *Fourth Rheumatism Review*: HENCH, P. S., BAUER, WALTER, GHRIST, DAVID, HALL, FRANCIS, HOLBROOK, W. P., KEY, J. A., and SLOCUMB, C. H.: The present status of rheumatism and arthritis; review of American and English literature for 1936, ANN. INT. MED., 1938, xi, 1089-1247.
5. *Fifth Rheumatism Review*: HENCH, P. S., BAUER, WALTER, DAWSON, M. H., HALL, FRANCIS, HOLBROOK, PAUL, and KEY, J. A.: The problem of rheumatism and arthritis; review of American and English literature for 1937, ANN. INT. MED., 1939, xii, 1005-1104; 1295-1374.
6. *Sixth Rheumatism Review*: HENCH, P. S., BAUER, WALTER, DAWSON, M. H., HALL, FRANCIS, HOLBROOK, W. P., KEY, J. A., and McEWEN, CURRIER: The problem of rheumatism and arthritis; review of American and English literature for 1938, ANN. INT. MED., 1940, xiii, 1655-1739; 1837-1990.
7. ABEL, O., JR., SIEBERT, W. J., and EARP, RALPH: Fibrositis, Jr. Missouri Med. Assoc., 1939, xxxvi, 435-437.
8. ABERCROMBIE, R. G.: Periarticular fibrositis of the shoulder, Brit. Jr. Rheumat., 1939, i, 236-248.

9. ABERCROMBIE, R. G.: The influence of morphological structure on the pathology of joints, *Ann. Rheumat. Dis.*, 1939, i, 99-108.
10. ADLERSBERG, DAVID, and ELLENBERG, MAX: Effect of carbohydrate and fat in the diet on uric acid excretion, *Jr. Biol. Chem.*, 1939, cxxviii, 379-385.
11. ADSON, A. W.: Chronic recurring sciatica; diagnosis and treatment of protrusions of ruptured intervertebral disks, *Arch. Phys. Therap.*, 1939, xx, 325-330.
12. AINLAY, G. W.: The use of bee venom in the treatment of arthritis and neuritis, *Nebraska Med. Jr.*, 1939, xxiv, 298-303.
13. ALBEE, F. H.: Extra-articular fusion of the hip joint for tuberculosis, *Am. Jr. Surg.*, 1939, xliv, 187-194.
14. ALBEE, F. H.: The present status of arthroplasty, *New York State Jr. Med.*, 1939, xxxix, 2118-2125.
15. ALBEE, F. H., and CAMPOS, O. P.: Low back pain and allied conditions, *Am. Jr. Surg.*, 1939, xliii, 386-393.
16. ALBRIGHT, FULLER, BLOOMBERG, ESTHER, and SMITH, PATRICIA H.: Post-menopausal osteoporosis, *Trans. Assoc. Am. Physicians*, 1940, lv, 298-305.
17. ALTMAN, H. S., and DAVIDSON, L. T.: Amyoplasia congenita (arthrogryposis multiplex congenita), *Jr. Pediat.*, 1939, xv, 551-557.
18. ALTSCHULE, M. D.: The relation between prolonged P-R interval and auricular fibrillation in patients with rheumatic heart disease, *Am. Heart Jr.*, 1939, xviii, 1-7.
19. ANDERSEN, LEONORA, and THEIS, RUTH: Serum phosphatase in arthritis with special reference to vitamin D therapy, *Med. Woman's Jr.*, 1939, xlv, 72-74.
20. ANDERSON, G. C., and WEXBERG, ERWIN: Protruded intervertebral disk; report of a case; note on a possible inflammatory etiologic factor (circumscribed arachnoiditis), *Arch. Surg.*, 1939, xxxix, 952-958.
21. ANDERSON, G. E., LAMB, A. E., BARRITT, A. S., JR., and NERB, LOUIS: The results of treatment of chronic atrophic (rheumatoid) arthritis with autogenous streptococcus filtrates selected on the basis of skin and joint sensitivity, *Brooklyn Hosp. Jr.*, 1939, i, 37-51.
22. ANDERSON, W. A. D.: Hyperparathyroidism and renal disease, *Arch. Path.*, 1939, xxvii, 753-778.
23. ANGLE, F. E., ALGIE, W. H., BAUMGARTNER, LEONA, and LUNSFORD, W. F.: Skin testing for brucellosis (undulant fever) in school children, *ANN. INT. MED.*, 1938, xii, 495-502.
24. ANSPACH, W. E., and CLIFTON, WILLIE MAE: Hyperparathyroidism in children; report of two cases, *Am. Jr. Dis. Child.*, 1939, lviii, 540-557.
25. ARMSTRONG, W. E. M.: The contribution of the bacteriologist to the rheumatic problem, *Brit. Jr. Rheumat.*, 1939, ii, 27-35.
26. ARTÉMIIEV, S.: Uniform working classification of acute rheumatism and diseases of joints of various origin, *Acta rheumatol.*, 1939, xi, 3-4.
27. ASCHOFF, LUDWIG: The rheumatic nodules in the heart, *Ann. Rheumat. Dis.*, 1939, i, 161-166.
28. ASCROFT, P. B.: Of the nervous sciatica: Dominicus Cotunnus, *Middlesex Hosp. Jr.*, 1939, xxxix, 38-45.
29. ASHERSON, N.: The association of infection of the ear with 'rheumatic' manifestations, *Rheumatism*, 1939, i, 38-41 (Oct.).
30. ATKINSON, F. R. B.: Still's disease, *Brit. Jr. Child. Dis.*, 1939, xxxvi, 100-114.
31. BACAL, H. L., and STRUTHERS, R. R.: Rheumatic infection in childhood: the effect of surgical operations on the blood sedimentation rate, *Canad. Med. Assoc. Jr.*, 1939, xl, 140-142.
32. BACH, FRANCIS: Dietetic aspects of rheumatism, *Brit. Jr. Rheumat.*, 1939, i, 173-189.
33. BACH, FRANCIS: Physiotherapy in fibrositis and the myalgias, *Brit. Jr. Phys. Med.*, 1939, ii, 108-112.

34. BACH, FRANCIS: Rheumatic diseases of the spine, *Clin. Jr.*, 1939, lxxviii, 227-235.
35. BACH, FRANCIS, HILL, N. G., PRESTON, T. W., and THORNTON, C. E.: Juvenile rheumatism in London, *Ann. Rheumat. Dis.*, 1939, i, 210-241.
36. BAILEY, E. T., and BURROWS, H. J.: Nail fixation of osteo-arthritic hip without exposure of joint, *Lancet*, 1939, i, 980-983.
37. BAIN, C. G.: Chronic (subclinical) undulant fever; report of a case, *Northwest Med.*, 1938, xxxvii, 395-396.
38. BAIRD, J. E.: American spa therapy in the treatment of rheumatoid diseases, *Jr. Missouri Med. Assoc.*, 1939, xxxvi, 272-274.
39. BAIRD, M. M.: Some remarks about "rheumatism," *Bull. Vancouver Med. Assoc.*, 1939, xv, 163-170.
40. BAKER, B. M.: The arthritis of bacillary dysentery, *Trans. Am. Climat. and Clin. Assoc.*, 1937, lii, 28-39.
41. BAKER, D. D., and BAILLIF, R. N.: Rôle of capsule in suprarenal regeneration studied with aid of colchicine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 117-121.
42. BALLENGER, E. G., ELDER, O. F., McDONALD, H. P., and COLEMAN, R. C.: Artificial fever in combination with sulfanilamide, *Urol. and Cutan. Rev.*, 1939, xliii, 441-443.
43. BANKS, S. W., and COMPERE, E. L.: Lesions of the intervertebral disk as related to backache and sciatic pain, *Surg. Clin. N. Am.*, 1939, xix, 43-58.
44. BARBER, C. G.: Osteochondrosis deformans tibiae, *Am. Jr. Roentgenol.*, 1939, xlii, 498-502.
45. BARR, J. S.: Intervertebral disk lesions as cause of sciatica, *Brit. Med. Jr.*, 1938, ii, 1247-1251.
46. BARTELS, E. C.: Sulfanilamide in undulant fever, *New England Jr. Med.*, 1938, ccxix, 988.
47. BARTELS, E. C.: The treatment of gout with a low-fat, high-carbohydrate diet, preliminary report, *New England Jr. Med.*, 1939, ccxx, 583-586.
48. BATTS, MARTIN, JR.: Rupture of the nucleus pulposus; an anatomical study, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 121-126.
49. BAUER, E. L.: Further studies on the treatment of chorea and rheumatic infection by fever induction, *Am. Jr. Med. Sci.*, 1939, cxcviii, 224-229.
50. BAUER, WALTER: Studies pertaining to the origin and nature of hypertrophic arthritis, *Trans. and Studies, Coll. Phys., Philadelphia*, 1939, vii, 1-20.
51. BAUER, WALTER: The diagnosis of the various arthritides, *New England Jr. Med.*, 1939, ccxxi, 524-533.
52. BAUER, WALTER, and COGGESHALL, H. C.: The treatment of gonococcal infections with sulfanilamide, sulfapyridine and allied compounds, *Med. Clin. North Am.*, 1939, xxiii, 1173-1191.
53. BEACH, E. W.: The cure of gonorrhea: an immunologic problem, *California and West. Med.*, 1939, li, 100-105.
54. BEARD, GERTRUDE: The physiological effects and technic of massage, *Physiotherapy Rev.*, 1939, xix, 67-75.
55. BEATTIE, C. P., BEATTIE, M. H., and ZAHAWI, S. A.: Brucellosis in Iraq, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1939, xxxiii, 173-182.
56. BEAUCHAMP, GUY: Osteopathy in rheumatic diseases, *Rheumatism*, 1939, i, 37-44 (Jan.).
57. BEAUCHAMP, GUY: Manipulation of the neck, *Rheumatism*, 1939, i, 36-38 (April).
58. BEAUCHAMP, GUY: Manipulation. II. Strapping for rheumatic joints, *Rheumatism*, 1939, i, 53-54 (July).
59. BEGGS, S. T.: The rheumatic problem, *Med. Officer*, 1938, ix, 281-282.
60. BEHRMAN, S., and FORMAN, L.: Dermatomyositis, *Proc. Roy. Soc. Med.*, 1939, xxxii, 1575-1577.
61. BELL, J. C.: The roentgen ray examination in individuals suffering from low back pain, *Kentucky Med. Jr.*, 1939, xxxvii, 185-186.

62. BENNETT, G. A., and SHAFFER, M. F.: The passage of proteins from the vascular system into joints and certain other body cavities, *Jr. Exper. Med.*, 1939, lxx, 277-291.
63. BENNETT, G. E., and COBEY, M. C.: Hemangioma of joints; report of five cases, *Arch. Surg.*, 1939, xxxviii, 487-500.
64. BERENS, CONRAD, ANGEVINE, D. M., GUY, LOREN, and ROTHBARD, SIDNEY: Eye lesions in experimental infections, special reference to arthritis, *Am. Jr. Ophth.*, 1938, xxi, 1315-1327.
65. BERG, SAMUEL: Unreliability of oxalated blood in determination of erythrocyte sedimentation rate, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 757-764.
66. BERGER, HERBERT: Intermittent hydrarthrosis with an allergic basis, *Jr. Am. Med. Assoc.*, 1939, cxii, 2402-2405.
67. BERGER, LOUIS: Synovial sarcomas in serous bursae and tendon sheaths, *Am. Jr. Cancer*, 1938, xxxiv, 501-539.
68. BERKHEISER, E. J.: Excision of the patella in arthritis of the knee joint, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2303-2307.
69. BHATIA, B. B.: A case of alkaptonuria associated with ochronosis and purpuric rashes, *Indian Med. Gaz.*, 1939, lxxiv, 160-161.
70. BIERMAN, WILLIAM, and HOROWITZ, E. A.: Combined heating technique for the treatment of gonorrhea in women, *Med. Rec.*, 1939, cxlix, 305-307.
71. BIERMAN, WILLIAM, and LEVENSON, C. L.: Fever therapy in gonococcal infections, *Radiology*, 1939, xxxii, 454-461.
72. BIGLER, J. A., and HARALAMBIE, J. Q.: Sulfanilamide and related compounds, a review of the literature, *Am. Jr. Dis. Child.*, 1939, lvii, 1110-1167.
73. BIGLER, J. A., and WERNER, MARIE: Cyanosis from use of sulfanilamide, *Am. Jr. Dis. Child.*, 1939, lvii, 1338-1342.
74. BILDERBACK, J. B., and OVERSTREET, R. M.: Incidence of rheumatic infections in children in Oregon, *Northwest Med.*, 1938, xxxvii, 390-393.
75. BISHOP, W. A.: Vertebral lesions in undulant fever, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 665-673.
76. BISHOP, W. A., JR.: Calcification of the supraspinatus tendon, cause, pathologic picture, and relation to scalenus anticus syndrome, *Arch. Surg.*, 1939, xxxix, 231-246.
77. BLAND, E. F., and JONES, T. D.: Natural history of rheumatic fever and heart disease, *Trans. Am. Climat. and Clin. Assoc.*, 1937, lii, 85-97.
78. BLAND, E. F., and JONES, T. D.: The delayed appearance of heart disease after rheumatic fever, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1380-1382.
79. BLANKENHORN, M. A.: Gonococcal arthritis in a child; differentiation from rheumatic fever. Treatment with sulphanilamide, *Jr. Med.*, 1939, xx, 80-81.
80. BLAU, ABRAM: Primary generalized myositis fibrosa; report of two cases with histopathology, *Jr. Mt. Sinai Hosp.*, 1938, v, 432-443.
81. BLAUCH, MARY B., and KOCH, F. C.: Application of the uricase method to the study of changes in vitro in the uric acid content of certain mammalian bloods, *Jr. Biol. Chem.*, 1939, cxxx, 455-469.
82. BLAUCH, MARY B., and KOCH, F. C.: A new method for the determination of uric acid in blood, with uricase, *Jr. Biol. Chem.*, 1939, cxxx, 443-454.
83. BLISS, ELEANOR A., FEINSTONE, W. H., GARRETT, ALICE W., and LONG, P. H.: Sulfapyridine and sulfanilamide in experimental pneumococcal, meningococcal, Welch bacillary and Friedländer's bacillary infections in mice, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 619-621.
84. BLUMGART, H. L., and GILLIGAN, DOROTHY R.: The treatment of undulant fever with sulfanilamide and related compounds, *Med. Clin. North Am.*, 1939, xxiii, 1193-1203.
85. BOEMER, L. C.: Infection, arthritis and allergy, *Laryngoscope*, 1939, xlix, 297-306.
86. BOEMER, L. C.: Infection, arthritis and allergy with an allergic dietary regimen, *Illinois Med. Jr.*, 1939, lxxv, 474-475.

87. BOOTH, G. C.: The psychological approach in therapy of chronic arthritis, *Rheumatism*, 1939, i, 48-59 (Jan.).
88. BOOTS, RALPH: Quoted by TEGNER, W. S.
89. BOSWORTH, DAVID: Tuberculosis of the osseous system; part I. Tuberculosis involving the spine, *Quart. Bull., Sea View Hosp.*, 1939, v, 85-116.
90. BOSWORTH, D. M., and HARE, C. C.: Herniation of the nucleus pulposus and hypertrophied ligamenta flava, *New York State Jr. Med.*, 1939, xxxix, 1739-1748.
91. BOWEN, W. H.: Suppuration in the hip joint, *Guy's Hosp. Rep.*, 1938, lxxxviii, 482-489.
92. BOYD, DOUGLAS, OSBORNE, S. L., and MARKSON, D. E.: Treatment of arthritis with acetyl-beta-methylcholine chloride, *Arch. Phys. Therap.*, 1939, xx, 406-410.
93. BRADFORD, F. K., and SPURLING, R. G.: Intraspinal causes of low back and sciatic pain; results in sixty consecutive low lumbar laminectomies, *Surg., Gynec. and Obst.*, 1939, lxix, 446-459.
94. BRANCH, H. E.: Low back pain, *Jr. Michigan Med. Soc.*, 1939, xxxviii, 499-501.
95. BRECK, L. W., and BASOM, W. C.: Bone and joint tuberculosis with special reference to its incidence and association with pulmonary tuberculosis, *Med. Rec.*, 1939, cl, 361-363.
96. BRISTOW, W. R.: Internal derangement of the knee joint, *Am. Jr. Surg.*, 1939, xliii, 458-465.
97. BRITISH RED CROSS SOCIETY CLINIC FOR RHEUMATISM: Report of the medical board for the year 1938, *Brit. Jr. Rheumat.*, 1939, i, 277-282.
98. BRØCHNER-MORTENSEN, KNUD: Uric acid in blood and urine, *Acta med. Scand.*, 1937 (suppl.), lxxxiv, 269 pp.
99. BRØCHNER-MORTENSEN, KNUD: On variations in the uric acid clearance after administration of purine, with special reference to the threshold problem, *Acta med. Scand.*, 1939, xcix, 525-537.
100. BRØCHNER-MORTENSEN, KNUD: Diagnosis of gout, *Acta med. Scand.*, 1939, xcix, 538-562.
101. BRODY, B. S.: Sciatic neuralgia, *Jr. Connecticut Med. Soc.*, 1939, iii, 66.
102. BROMBERG, LEON: Artificial fever therapy, *Jr. Missouri Med. Assoc.*, 1939, xxxvi, 24-31.
103. BROOKS, CLYDE: The toxic effects of sulfanilamide and sulfapyridine, *New Orleans Med. and Surg. Jr.*, 1939, xcii, 115-118.
104. BROOKS, CLYDE: A new technique for the blood sedimentation test, *Jr. Med. Assoc. Alabama*, 1939, ix, 72-73.
105. BROWN, A. E.: The use of sulfanilamide and related compounds, *Med. Clin. N. Am.*, 1939, xxiii, 927-944.
106. BROWN, H. A.: Nucleus pulposus rupture and its relation to injury—neurosurgical aspect, *California and West. Med.*, 1939, li, 297-298.
107. BROWN, H. R., JR., and CLARK, W. F.: Plasma specific gravity and control of fluid administration in artificial fever, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 490-494.
108. BROWN, W. H., THORNTON, W. B., and WILSON, J. S.: Observations on the absorption, distribution and excretion of sulphapyridine, dajenan or M. & B. 693, *Jr. Clin. Invest.*, 1939, xviii, 803-819.
109. BROWNING, W. H., and SHAVIN, J. S.: Undulant fever—a problem in every physician's practice, *New Orleans Med. and Surg. Jr.*, 1939, xcii, 81-87.
110. BRUCE, G. M.: Retinitis in dermatomyositis, *Trans. Am. Ophth. Soc.*, 1938, xxxvi, 282-297.
111. BRUETSCH, W. L.: The histopathology of the psychoses with subacute bacterial and chronic verrucose rheumatic endocarditis, *Am. Jr. Psychiat.*, 1938, xcv, 335-346.
112. BRUETSCH, W. L., and BAHR, M. A.: Chronic rheumatic brain disease as a factor in the causation of mental illness; report of two cases, *Jr. Indiana Med. Assoc.*, 1939, xxxii, 445-450.
113. BRUGSCH, HEINRICH, and PRATT, J. H.: Short wave and ultra short wave diathermy, *Am. Jr. Med. Sci.*, 1939, cxvii, 653-663.

114. BRUMBAUGH, H. L.: Rupture of the supraspinatus, *Ohio State Med. Jr.*, 1939, xxxv, 597-599.
115. BUCHANAN, J. S.: Pyogenic infections of the foot, *Med. Press*, 1939, ccii, 374-377.
116. BUCKLEY, C. W.: Treatment of arthritis in the spa, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 250-255.
117. BUCKLEY, C. W.: Advances in the treatment of rheumatic diseases, *Practitioner*, 1939, cxliii, 376-383.
118. BUNTING, G. L.: Experiences in a local vaccine clinic, *Rheumatism*, 1939, i, 42-43 (Oct.).
119. BURBANK, REGINALD: An outline of the aetiology, pathology, and treatment of arthritis, *Tri-State Med. Jr.*, 1939, xii, 2355.
120. BUREAU OF INVESTIGATION: Zorbit a fake capitalized at forty thousand dollars, *Jr. Am. Med. Assoc.*, 1939, cxii, 2453.
121. BURKHART, ELIZABETH Z.: Colchicine reactions in ventral prostate of castrated male rats following androgenic treatment, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 137-139.
122. BURMAN, M. S., and KLING, D. H.: The excretion of the dye Evans blue into the synovial effusion of rheumatoid arthritis, *Acta rheumatol.*, 1939, xi, 1-3.
123. BURNS, B. H.: Fixation of the osteo-arthritic hip by nailing, *Lancet*, 1939, i, 978-980.
124. BURR, R. C.: Osteochondritis dissecans, *Canad. Med. Assoc. Jr.*, 1939, xli, 232-235.
125. BURROWS, ARTHUR (with pathological report by H. M. TURNBULL): Cutis hyperelastica (Ehlers-Danlos syndrome), *Brit. Jr. Dermat.*, 1938, l, 648-652.
126. BURT, J. B.: Heberden's nodes in a girl of fifteen years of age, *Rheumat. Dis.*, 1939, i, 52-56.
127. BURT, J. B.: The diagnosis and treatment of trunk sciatica, *Practitioner*, 1939, cxliii, 275-285.
128. BURT, J. B., and GORDON, R. G.: Gout an unsolved problem, *Ann. Rheumat. Dis.*, 1939, i, 304-318.
129. BYNUM, W. T.: Recurrences of undulant fever (brucellosis) following the administration of sulfanilamide, *Jr. Am. Med. Assoc.*, 1939, cxii, 835-836.
130. CADDEN, J. F., and STANDER, H. J.: Uric acid metabolism in eclampsia, *Am. Jr. Obst. and Gynec.*, 1939, xxxvii, 37-47.
131. CALDER, R. M.: Chronic brucellosis, *South. Med. Jr.*, 1939, xxxii, 451-460.
132. CALDER, R. M., STEEN, CHRISTINE, and BAKER, LAURENCE: Blood studies in brucellosis, *Jr. Am. Med. Assoc.*, 1939, cxii, 1893-1898.
133. CALDWELL, G. A.: Sulfanilamide in gonorrheal arthritis, *Tri-State Med. Jr.*, 1939, xii, 2358-2360.
134. CALLAHAN, E. J., and INGHAM, D. W.: Gout; report of nine cases with a new addition to the treatment, *Med. Rec.*, 1939, cxlix, 167-168.
135. CALTHROP, G. T.: Dental radiology in rheumatism, *Rheumatism*, 1938, i, 44-46 (July).
136. CAMP, J. D.: The roentgenologic diagnosis of intraspinal protrusion of intervertebral disks, by means of radiopaque oil, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2024-2029.
137. CAMPBELL, W. C.: Reconstruction of the ligaments of the knee, *Am. Jr. Surg.*, 1939, n.s. xliii, 473-480.
138. CAMPBELL, W. C.: Repair of the anterior cruciate ligament of the knee, *South. Med. Jr.*, 1939, xxxii, 442-445.
139. CAMPBELL, W. C.: Surgical measures in the residual stage of arthritis, *Tri-State Med. Jr.*, 1939, xii, 2361-2362; 2366.
140. CARLETON, ALICE: A note on the effect of colchicine on the skin of young rats, *Jr. Anat.*, 1939, lxxiii, 416-418.
141. CARLSON, C. E.: Painful shoulders, *Northwest Med.*, 1939, xxxviii, 52-55.
142. CARTER, R. E. B.: Two cases of dermatomyositis, *Proc. Roy. Soc. Med.*, 1938, xxxii, 89-92.
143. CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL: Case 25141, *New England Jr. Med.*, 1939, ccxx, 600-604.

144. CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL: Case 25161, *New England Jr. Med.*, 1939, ccxx, 670-674.
145. CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL: Case 25231, *New England Jr. Med.*, 1939, ccxx, 964-967.
146. CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL: Case 25261, *New England Jr. Med.*, 1939, ccxx, 1082-1085.
147. CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL: Case 25312, *New England Jr. Med.*, 1939, ccxxi, 196-198.
148. CATHELL, E. J.: Review of recent literature on sulfanilamide, with reports on its use in peritonitis, *South. Med. and Surg.*, 1939, ci, 7-9.
149. CECIL, R. L., ANGEVINE, D. M., and ROTHBARD, SIDNEY: Experimental arthritis in rabbits produced with streptococci and other organisms, *Am. Jr. Med. Sci.*, 1939, cxcviii, 463-475.
150. CHALMERS, R. W.: Chronic arthritis of the lumbar spine, with its differential diagnosis and treatment, *Brit. Jr. Rheumat.*, 1939, ii, 35-46.
151. CHAMBERLAIN, W. E.: Low back pain, *Proc. California Acad. Med.* (1937-1938), 1939, pp. 41-96.
152. CHEETHAM, J. G.: A study of the newer agencies used in the treatment of gonorrhea, with special reference to sulfanilamide and to hyperpyrexia, *Urol. and Cutan. Rev.*, 1939, xliii, 314-319.
153. CHINN, B. D.: The use of sulfanilamide in experimental brucellosis, *Jr. Infect. Dis.*, 1939, lxiv, 78-82.
154. CHITTY, HUBERT: Interesting case of Charcot's joint, *Brit. Jr. Surg.*, 1939, xxvii, 183-185.
155. CHOLMELEY, J. A.: Distribution and treatment of extra-articular foci in tuberculous arthritis of the hip-joint, *Brit. Jr. Surg.*, 1939, xxvii, 224-233.
156. CHOPRA, R. N., BASU, B. C., and SEN, S.: Rat-bite fever in Calcutta, *Indian Med. Gaz.*, 1939, lxxiv, 449-451.
157. CLAHR, JACOB, GREENSTEIN, N. M., and KLEIN, M. D.: Circulation time studies in pregnant women with rheumatic heart disease, *Am. Jr. Obst. and Gynec.*, 1939, xxxviii, 39-47.
158. CLARK, A. L.: Sulfanilamide in treatment of nonspecific infections of the urinary tract, *Jr. Am. Med. Assoc.*, 1939, cxii, 719-723.
159. CLEVELAND, MATHER: Surgical fusion of unstable joints due to neuropathic disturbance, *Am. Jr. Surg.*, 1939, n.s. xliii, 580-584.
160. CLEVELAND, MATHER: Surgical treatment of joint tuberculosis, *Jr. Bone and Joint Surg.*, 1939, xxi, 607-618.
161. CLOWARD, R. B.: Low-back pain and sciatica; etiology, pathology and surgical treatment, *Trans. Hawaii Territor. Med. Assoc.*, 1939, pp. 113-120.
162. COBB, STANLEY, BAUER, WALTER, and WHITING, ISABEL: Environmental factors in rheumatoid arthritis; a study of the relationship between the onset and exacerbations of arthritis and the emotional or environmental factors, *Jr. Am. Med. Assoc.*, 1939, cxiii, 668-670.
163. COBURN, A. F., and MOORE, LUCILE V.: The prophylactic use of sulfanilamide in streptococcal respiratory infections, with especial reference to rheumatic fever, *Jr. Clin. Invest.*, 1939, xviii, 147-155.
164. COBURN, A. F., and PAULI, RUTH H.: The significance of prolonged streptococcal antibody development in rheumatic fever, *Jr. Clin. Invest.*, 1939, xviii, 141-145.
165. COBURN, A. F., and PAULI, RUTH H.: A precipitinogen in the serum prior to the onset of acute rheumatism, *Jr. Exper. Med.*, 1939, lxix, 143-162.
166. COCHRANE, W. A.: Orthopaedic aspects of sciatica, *Brit. Med. Jr.*, 1938, ii, 1251-1253.
167. COGAN, J. V.: Relation of gingival infection to arthritis, *Jr. Am. Dent. Assoc.*, 1939, xxvi, 56-60.

168. COGGESHALL, H. C., and BAUER, WALTER: The treatment of gonorrheal and rheumatoid arthritis with sulfanilamide, *New England Jr. Med.*, 1939, ccxx, 85-103.
169. COHN, ALFRED: Notes on the microscopic diagnosis and cultural differentiation of the gonococcus, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 986-988.
170. COHN, ALFRED: The gonococcus complement fixation test in gonococcal infections treated with sulfanilamide, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1939, xxiii, 461-476.
171. COKE, HARRY: Some principles of chrysotherapy, *Rheumatism*, 1938, i, 37-41 (July).
172. COKE, HARRY: The differential sedimentation test in rheumatism, *Rheumatism*, 1939, i, 47-50 (April).
173. COKE, HARRY: The differential sedimentation test—II, *Rheumatism*, 1939, i, 49-52 (July).
174. COKE, HARRY: The differential sedimentation rate—III, *Rheumatism*, 1939, i, 32-37 (Oct.).
175. COLLIER, W. A.: Infectious polyarthritis of rats, *Jr. Path. and Bact.*, 1939, xlviii, 579-589.
176. COLLINS, D. H.: The peripheral circulation in rheumatism, *Harrogate Spa Med. Jr.*, 1938, i, 8-14.
177. COLLINS, D. H.: Observations on the pathology of acute rheumatism and rheumatoid arthritis, *Rheumat. Dis.*, 1939, i, 38-45.
178. COLLINS, D. H.: The pathology of osteoarthritis, *Brit. Jr. Rheumat.*, 1939, i, 248-262.
179. COLLINS, D. H., ERNEST, M. M., and WOODMANSEY, A.: The medical uses of the local contrast bath, *Harrogate Spa Med. Jr.*, 1939, ii, 4-8.
180. COLLINS, D. H., GIBSON, H. J., RACE, J., and SALT, H. B.: The erythrocyte sedimentation test: a wide-bore tube method using oxalated blood and permitting correction of the result to a standard red-cell volume, *Ann. Rheumat. Dis.*, 1939, i, 333-358.
181. COLLINS, R. T.: Transitory neurological changes during hyperthermia, *Bull. Neurol. Inst. New York*, 1938, vii, 291-296; *Med. Rec.*, 1939, cl, 92-96.
182. COLLINS, VERA L.: The relation of liver and gallbladder disease to arthritis, *Rev. Gastroenterol.*, 1939, vi, 344-349.
183. COLLIS, W. R. F.: Bacteriology of rheumatic fever, *Lancet*, 1939, ii, 817-820.
184. COMROE, B. I.: Sulphur therapy in arthritis, with a review of the literature, *Medicine* 1939, xviii, 203-219.
185. CONDELL, L. A.: Sulfanilamide in treatment of brucellosis, *Southwestern Med.*, 1939, xxiii, 173-176.
186. CONTRATTO, A. W., and LEVINE, S. A.: Acute lupus erythematosus disseminatus; report of a case, *New England Jr. Med.*, 1939, ccxxi, 602-604.
187. CONTRELL, R. G.: The relation of the liver to arthritis, *Med. Press*, 1939, cci, 180-182.
188. COPLAND, S. M., and MICHEL, MARSHALL: Peritendinitis calcarea, *New Orleans Med. and Surg. Jr.*, 1939, xcii, 261-265.
189. CORBIN, K. B., and HINSEY, J. C.: Influence of the nervous system on bone and joints, *Anat. Rec.*, 1939, lxxv, 307-317.
190. CORBUS, B. C., JR.: The pathology of the complications of neisserian infection in the male and their surgical treatment, *Surg. Clin. N. Am.*, 1939, xix, 191-202.
191. CORBUS, B. C., and CORBUS, B. C., JR.: The serological control of neisserian infections by means of the bouillon filtrate (Corbus-Ferry); a further report, *Illinois Med. Jr.*, 1939, lxxv, 19-28.
192. CORR, PHILIP, and ROOT, R. N.: Death from granulocytopenia after sulfanilamide therapy, *Jr. Am. Med. Assoc.*, 1939, cxii, 1939-1940.
193. COULTER, J. S.: Short wave diathermy, *Med. Clin. N. Am.*, 1939, xxiii, 121-137.
194. COULTER, J. S.: Physical therapy in general practice, *Wisconsin Med. Jr.*, 1939, xxxviii, 466-470.
195. COULTER, J. S., and OSBORNE, S. L.: Short wave medical diathermy; clinical applications, *New York State Jr. Med.*, 1939, xxxix, 699-705.

196. COUNCIL ON PHARMACY AND CHEMISTRY: Aciform II not acceptable for N. N. R., Jr. Am. Med. Assoc., 1939, cxii, 2517.
197. COUNCIL ON PHYSICAL THERAPY: Medical diathermy, Jr. Am. Med. Assoc., 1939, cxii, 2046-2049.
198. COVENTRY, W. D.: Granulocytopenia, Minnesota Med., 1939, xxii, 177-179.
199. COXON, R. V., and FORBES, J. R.: Agranulocytic angina following administration of M. & B. 693, Lancet, 1938, ii, 1412-1413.
200. CRAIG, W. MCK.: Treatment of intractable sciatic pain due to protruded intervertebral discs, Am. Jr. Surg., 1939, n.s. xlv, 499-506.
201. CRAIG, W. MCK., and WALSH, M. N.: The diagnosis and treatment of low back and sciatic pain caused by protruded intervertebral disk and hypertrophied ligaments, Minnesota Med., 1939, xxii, 511-517.
202. CRAWFORD, M. D.: The effect of labour on plasma uric acid and urea, Jr. Obst. and Gynaec. Brit. Emp., 1939, xlv, 540-553.
203. CREER, W. S.: Physiotherapy and orthopaedics, Brit. Jr. Phys. Med., 1938, i, 420; 1939, ii, 17, 47, 75.
- 203a. CRICHTON-MILLER, H.: Psychological factors in physiotherapy, Brit. Jr. Phys. Med., 1939, ii, 43-46.
204. CROTTI, ANDRÉ: Hyperparathyroidism in hyperthyroidism, Trans. Internat. Coll. Surg., 1938, i, 141-157.
205. CROWE, H. W.: Comments on vaccine treatment, Rheumatism, 1938, i, 25-27 (July).
206. CROWE, H. W.: Stock vaccine in the treatment of chronic rheumatic disease, Rheumatism, 1939, i, 24-34 (July).
207. CROWE, H. W., IRVINE, L. C. D., and COKE, HARRY (Section on manipulation by Guy Beauchamp): Rheumatism, Jr. Roy. Nav. Med. Serv., 1939, xxv, 232-249.
208. CURRENT COMMENT: Drugs in treatment of arthritis, Jr. Am. Med. Assoc., 1938, cxi, 1662.
209. CUTBILL, L. J.: An index of the sedimentation rate on a mathematical basis, Ann. Rheumat. Dis., 1939, i, 359-363.
210. CYRIAX, JAMES: Rheumatic headache, Brit. Med. Jr., 1938, ii, 1367-1368.
211. DACSO, MICHAEL: Disturbances of peripheral blood circulation in chronic rheumatic diseases, Rheumatism, 1938, i, 72-76 (Oct.).
212. DAIL, C. W., and MOOR, F. B.: Undergraduate education in physical therapy, Arch. Phys. Therap., 1939, xx, 215-219.
213. DALLY, J. F. H.: The problem of the rheumatic child, Rheumatism, 1939, i, 19-24 (Oct.).
214. DANIEL, W. E.: A comparison of sulfanilamide, sulfanilyl-sulfanilamide and sulfapyridine, South. Med. and Surg., 1939, ci, 542-543.
215. DARDINSKI, V. J., and LYDDANE, E. S.: Agranulocytic angina; report of a case due to causalin, Jr. Am. Med. Assoc., 1939, cxii, 134.
216. DARRACH, WILLIAM: Chondritis of knee, Ann. Surg., 1939, cx, 948-950.
217. DAVIDSON, L. S. P.: The rheumatic problem; a plea for a national campaign against the rheumatic diseases, Practitioner, 1939, cxliii, 237-245.
218. DAVIS, K. S.: Intraspinal protrusions of the intervertebral discs: roentgenographic findings, California and West. Med., 1939, li, 230-234.
219. DAVISON, H. M., LOWANCE, M. I., and CROWE, W. R.: Arthritis: Treatment by hyperpyrexia, Jr. Med. Assoc. Georgia, 1939, xxviii, 245-246; 262.
220. DAWSON, M. H., and BOOTS, R. H.: Arthritis associated with lymphogranuloma venereum, Jr. Am. Med. Assoc., 1939, cxiii, 1162-1163.
221. DAWSON, M. H., and HOBBS, G. L.: Rat-bite fever, Trans. Assoc. Am. Physicians, 1939, liv, 329-332.
222. DEBDAS, N.: Can rheumatic fever cause melena? Indian Jr. Pediat., 1939, vi, 57-61.
223. DE SANTO, D. A., and WILSON, P. D.: Xanthomatous tumors of joints, Jr. Bone and Joint Surg., 1939, xxi, 531-558.

224. DEUCHER, W. G., and LOVE, J. G.: Posterior protrusions of the intervertebral disks: pathologico-anatomic aspects, *Proc. Staff Meet. Mayo Clin.*, 1938, xiii, 697-700.
Pathologic aspects of posterior protrusions of the intervertebral disks, *Arch. Path.*, 1939, xxvii, 201-211.
225. DIACK, A. W., and TROMMALD, J. P.: De Quervain's disease, a frequently missed diagnosis, *West. Jr. Surg.*, 1939, xlvii, 629-633.
226. DICKSON, F. D.: Discussion, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2404.
227. DIENES, LOUIS: L organisms of Klieneberger and Streptobacillus moniliformis, *Jr. Infect. Dis.*, 1939, lxxv, 24-42.
228. DIENES, L., and SULLIVAN, E. R.: Morphology and nature of pleuropneumonia-like microorganisms, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 424-426.
229. DIGILIO, V. A., and PESCATORE, J. A.: Mitral stenosis of rheumatic origin; usual and unusual features, *Delaware State Med. Jr.*, 1939, xi, 158-162.
230. DIGILIO, V. A., and PESCATORE, J. A.: Abdominal pain on locomotion in rheumatic disease; its significance in the past medical history, *Pennsylvania Med. Jr.*, 1939, xliii, 33-35.
231. DITTRICH, R. J.: Low back pain and spina bifida occulta, *Am. Jr. Surg.*, 1939, xliii, 739-745.
232. DOLMAN, C. E., HUDSON, VIVIENNE, and MATHIAS, D. G. B.: Further observations on brucellosis in and around Vancouver, *Canad. Pub. Health Jr.*, 1939, xxx, 100-104.
233. DONOHUE, W. L.: Pathology of the intervertebral disc, *Am. Jr. Med. Sci.*, 1939, cxcviii, 419-437.
234. DOUTHWAITE, A. H.: Discussion on manipulation in rheumatic disorders, *Proc. Roy. Soc. Med.*, 1939, xxxii, 273-275.
235. DOWLING, G. B.: Two cases of diffuse scleroderma, sclerodactylia and myositis, *Proc. Roy. Soc. Med.*, 1939, xxxii, 255-260.
236. DOWLING, G. B., and GRIFFITHS, W. J.: Dermatomyositis and progressive scleroderma, *Lancet*, 1939, i, 1424-1428.
237. DUNBAR, F.: Character and symptom formation; some preliminary notes with special reference to patients with hypertensive, rheumatic and coronary disease, *Psychanalyt. Quart.*, 1939, viii, 18-47.
238. DUTHIE, J. J. R.: The sociological aspects of the treatment of arthritis; notes on a visit to the United States, *Ann. Rheumat. Dis.*, 1939, i, 201-209.
239. DYSON, C. B.: Some incidental observations on the possibility of virus as part causal factor in rheumatism, *Rheumat. Dis.*, 1939, i, 15-17.
240. EAGLES, G. H.: A virus in rheumatism, *Rheumat. Dis.*, 1939, i, 18-26.
241. EAGLES, G. H., and BRADLEY, W. H.: The agglutination of suspensions of virus-like particles prepared from exudates in acute rheumatic fever, *Quart. Jr. Med.*, 1939 n.s. viii, 173-184.
242. EARLE, K. V.: Sulphanilamide derivatives in the treatment of tropical pyomyositis, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1939, xxxiii, 169-172.
243. ECHTMAN, JOSEPH: The present status of short wave therapy, *Jr. Am. Inst. Homeop.*, 1939, xxxii, 525-539.
244. EDGEcombe, W.: On the prescribing of baths, *Harrogate Spa Med. Jr.*, 1938, i, 1-5.
245. EDGEcombe, WILFRID: Gout and the chronic rheumatic diseases, *Rheumatism*, 1938, i, 61-67 (Oct.).
246. Editorial: Haverhill fever (erythema arthriticum epidemicum), *Jr. Am. Med. Assoc.*, 1939, cxiii, 941-942.
247. Editorial: Saltrag for arthritis, *Minnesota Med.*, 1939, xxii, 321.
248. Editorial: Rheumatism, 1940, ii, 94.
249. EDMUNDS, L. H.: Common injuries involving the knee joint, *Northwest Med.*, 1939, xxxviii, 85-91.
250. EIDINOW, ALBERT: X-ray treatment of the spondylitis and the rheumatic diseases, *Brit. Jr. Rheumat.*, 1939, ii, 13-20.

251. ELDER, A. V.: The therapeutic scope of a sea voyage, *Med. Press*, 1938, cxcvii, 113-116.
252. ELGHAMMER, H. W.: Treatment of rheumatic fever in children, *Illinois Med. Jr.*, 1939, lxxvi, 527-530.
253. ELKINS, E. C., and KRUSEN, F. H.: Clinical results of fever therapy, *Arch. Phys. Therap.*, 1939, xx, 346-353; 376.
254. ELLISTON, G. S.: The fight against rheumatism; the role of the state, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 568-573.
255. ELLMAN, PHILIP: Drug treatment in the chronic rheumatic diseases, *Brit. Jr. Rheumat.*, 1939, i, 263-277.
256. ELWARD, J. F.: Motion in the vertebral column, *Am. Jr. Roentgenol.*, 1939, xlii, 91-99.
257. EMPIRE RHEUMATISM COUNCIL: Royal president's address at Mansion House, *Ann. Rheumat. Dis.*, 1939, i, 150-160.
258. EPSTEIN, ERVIN: Differential diagnosis of keratosis blennorrhagica and psoriasis arthropathica, *Arch. Dermat. and Syph.*, 1939, xl, 547-559.
259. EVANS, ALICE C.: The chronic brucellosis patient, *Am. Jr. Nursing*, 1939, xxxix, 113-116.
260. EVANS, ALICE C.: Difficulties in the diagnosis of chronic brucellosis, *Am. Jr. Trop. Med.*, 1939, xix, 319-325.
261. EWALD, C. A.: Water bed for the bedridden, *Northwest Med.*, 1938, xxxvii, 397.
262. FABER, H. K., SMITH, C. E., and DICKSON, E. C.: Acute coccidioidomycosis with erythema nodosum in children, *Jr. Pediat.*, 1939, xv, 163-171.
263. FANTUS, BERNARD: The therapy of the Cook County Hospital, *Jr. Am. Med. Assoc.*, 1939, cxiii, 676-680.
264. FARBMAN, A. A., SANDWEISS, D. J., and SALTZSTEIN, H. C.: The effect of pregnancy and of antuitrin-S on cinchophen ulcers in dogs, *Am. Jr. Digest. Dis.*, 1939, vi, 702-703.
265. FARKAS, ALADÁR: A new operative treatment of tuberculous coxitis in children, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 323-333.
266. FARLEY, R. T.: The influence of prolonged administration of high dosages of vitamin D upon the serum calcium of adults, *Journal-Lancet*, 1939, lix, 401-404.
267. FARRELL, ELLISTON, LORDI, G. H., and VOGEL, JOSEPH: Haverhill fever; report of a case with review of the literature, *Arch. Int. Med.*, 1939, lxiiv, 1-14.
268. FARRELL, J. I.: The treatment of gonococcal infections with sulfanilamide, *Jr. Urol.*, 1939, xli, 44-50.
269. FERDERBER, M. B.: Report on the second year of fever therapy research by the department of industrial hygiene, School of Medicine, University of Pittsburgh, 1939.
270. FERGUSON, J. H.: The clotting of hemophilic plasma by thromboplastic enzyme, *Am. Jr. Physiol.*, 1939, cxxvi, 669-672.
271. FERNANDO, P. B.: Rheumatic heart disease as met with in hospital practice in Ceylon, *Quart. Jr. Med.*, 1939, n.s. viii, 261-275.
272. FINCHER, E. F.: Neurologic aspects of low back pain and sciatica, *Ann. Surg.*, 1939, cix, 1028-1033.
273. FINDLAY, G. M., MACKENZIE, R. D., MACCALLUM, F. O., and KLIENEBERGER, EMMY: The aetiology of polyarthritis in the rat, *Lancet*, 1939, ii, 7-10.
274. FINKELSTEIN, WILLIAM: Fever therapy at high humidities, *Arch. Phys. Therap.*, 1938, xix, 748-752; 762.
275. FISHBAUGH, E. C.: Colon disease and its therapy in relation to chronic arthritis, *Arch. Phys. Therap.*, 1939, xx, 411-415.
276. FISHER, A. G. T.: A contribution to the pathology of the rheumatoid type of arthritis and of rheumatic fever (Abst.), *Rheumat. Dis.*, 1939, i, 46-52.
277. FISHER, A. G. T.: The structure and functions of synovial membrane and articular cartilage, *Brit. Med. Jr.*, 1939, ii, 390-393.
278. FISHER, A. G. T.: Orthopaedic and surgical aspects of chronic rheumatism, *Practitioner*, 1939, cxliii, 286-296.

279. FITZ, REGINALD, PARKS, HARRY, and BRANCH, C. F.: Periarthritis nodosa; report of a case, *Arch. Int. Med.*, 1939, lxiv, 1133-1155.
280. FLEISCHMANN, W.: The use of colchicine in the assay of androgens, *Endocrinology*, 1939, xxv, 798-800.
281. FLEMING, ALEXANDER: Serum and vaccine therapy in combination with sulphanilamide or M and B 693, *Proc. Roy. Soc. Med.*, 1939, xxxii, 911-920.
282. FLETCHER, ERNEST: The value of sulphur and iodine in the treatment of chronic arthritis, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 104-111.
283. FLETCHER, ERNEST: Osteoarthritis; an attempt to elucidate the aetiology and pathogenesis of the condition by clinical study and analysis, *Brit. Jr. Rheumat.*, 1939, ii, 62-111.
284. FLIPPIN, H. F.: Undulant fever: diagnosis and modern methods of treatment, *Med. Rec.*, 1939, cxlix, 159-161.
285. FORESTIER, JACQUES: The importance of sacro-iliac changes in the early diagnosis of ankylosing spondylarthritis; Marie-Strümpell-Bechterew disease, *Radiology*, 1939, xxxiii, 389-402.
286. FOX, F.: Industry and rheumatism, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 368-373.
287. FOX, T. T., BURMAN, M. S., and SINBERG, SAMUEL: An unusual case of tuberculosis of the spine, *Am. Rev. Tuberc.*, 1939, xxxix, 825-829.
288. FRANKAU, CLAUDE: The principles of treatment in gunshot wounds of joints, *Brit. Med. Jr.*, 1939, ii, 27-28.
289. FRANKEL, E. L.: Treatment of sprains by injection of procaine, *Lancet*, 1939, ii, 597.
290. FREIBERG, J. A.: Low back pain; correlation of some of the signs and symptoms, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2195-2198.
291. FREUND, ERNST: Osteochondritis dissecans of the head of the femur; partial idiopathic aseptic necrosis of the femoral head, *Arch. Surg.*, 1939, xxxix, 323-352.
292. FREUND, ERNST: Joint cartilage under infraphysiologic, ultraphysiologic and euphysiologic demands, *Arch. Surg.*, 1939, xxxix, 596-623.
293. FREYBERG, R. H., BLOCK, W. D., and FROMER, M. F.: A study of sulfur metabolism and the effect of sulfur administration in chronic arthritis, *Jr. Clin. Invest.*, 1940, xix, 423-435.
294. FRIEDEN, E.: Fever therapy for children; nursing care and management, *Am. Jr. Nursing*, 1939, xxxix, 762-767.
295. FRIEDMAN, E. D.: Neurologic aspects of backache, *New York State Jr. Med.*, 1939, xxxix, 1734-1738.
296. FRIPP, A. T.: A method of shortening convalescence; the Fripp McConnel foot-rest, *Rheumatism*, 1939, i, 41-47 (April).
297. FUNSTEN, R. V.: Acute and remote effects of injuries to the knee joint, *West Virginia Med. Jr.*, 1939, xxxv, 323-326.
298. FURNISS, AUSTIN: Some common dermatological conditions and their treatment; psoriasis, *Prescriber*, 1939, xxxiii, 148-151.
299. FUTCHER, P. H., and SCOTT, V. C.: Four cases of gonococcal endocarditis treated with sulfanilamide, with recovery of one, *Bull. Johns Hopkins Hosp.*, 1939, lxxv, 377-391.
300. GARDEN, R. S.: Ossification in the anterior cruciate ligament, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 1027.
301. GARVIN, C. F.: Complications following the administration of sulfanilamide, *Jr. Am. Med. Assoc.*, 1939, cxiii, 288-290.
302. GASKING, C. T.: Observations on blood platelets during chrysotherapy in rheumatoid arthritis, *Harrogate Spa Med. Jr.*, 1939, ii, 9-16.
303. GAULD, R. L., CIOCCO, ANTONIO, and READ, FRANCES E. M.: Further observations on the occurrence of rheumatic manifestations in the families of rheumatic patients, *Jr. Clin. Invest.*, 1939, xviii, 213-217.

304. GEORGE, E. M.: Spondylolisthesis, Surg., Gynec. and Obst., 1939, lxxviii, 774-781.
305. GERSH, ISADORE, and BLACK, W. C.: Histology of the cutaneous reaction to *Brucella melitensis* antigen, Arch. Path., 1939, xxvii, 307-312.
306. GESCHICKTER, C. F., and MASERITZ, I. H.: Affections of muscles, Jr. Bone and Joint Surg., 1939, xxi, 576-594.
307. GHORMLEY, J. W.: Bursitis, Am. Jr. Surg., 1939, n.s. xliv, 282-292.
308. GHORMLEY, J. W., and SILVERGLADE, ALEXANDER: Circulation of the joints of chronic arthritis, New York State Jr. Med., 1939, xxxix, 1489-1497.
309. GIANNESTRAS, N. J.: Surgical treatment of Charcot joint, Jr. Med., 1939, xx, 392-395.
310. GIBSON, H. J.: The role of clinical pathology in the management of chronic rheumatism, Jr. Roy. Inst. Pub. Health and Hyg., 1939, ii, 286-298.
311. GIBSON, N. M., and WILEY, C. J.: Sulphonamide chemotherapy in gonorrhea, Med. Jr. Australia, 1939, i, 686-688.
312. GIBSON, STANLEY: Pathology of rheumatic fever, Illinois Med. Jr., 1939, lxxvi, 530-536.
313. GILCREEST, E. L., and ALBI, PIERO: Unusual lesions of muscles and tendons of the shoulder girdle and upper arm, Surg., Gynec. and Obst., 1939, lxxviii, 903-917.
314. GILES, UPTON: The historic development and modern application of artificial fever, New Orleans Med. and Surg. Jr., 1939, xci, 655-669.
315. GILL, A. B.: Stiff elbow, Surg. Clin. N. Am., 1938, xviii, 1663-1669.
316. GILMOUR, JOHN: Adolescent deformities of the acetabulum; an investigation into the nature of protrusio acetabuli, Brit. Jr. Surg., 1939, xxvi, 670-699.
317. GILMOUR, JOHN: The relationship of acetabular deformity to spontaneous osteo-arthritis of the hip-joint; an investigation of the intra-articular factors which predispose to osteo-arthritic degeneration, Brit. Jr. Surg., 1939, xxvi, 700-704.
318. GIRDLESTONE, G. R.: Traumatic synovitis and injuries to the ligaments of the knee-joint, Brit. Med. Jr., 1939, ii, 1050-1052.
319. GLASPEL, C. J.: Penetrating foreign body wounds of the knee joint, Journal-Lancet, 1939, lix, 56-57.
320. GLASS, V., and KENNETT, S. J.: The effect of various forms of particulate carbon on the growth of the gonococcus and meningococcus, Jr. Path. and Bact., 1939, xlix, 125-133.
321. GLOVER, J. A.: Control of common fevers; rheumatic fever, Lancet, 1939, i, 465-468.
322. GLOVER, J. A.: Quoted by Elliston, G. S.
323. GOFF, C. W.: Localization of pain in back injuries, Jr. Connecticut Med. Soc., 1939, iii, 345-346.
324. GOLDBERGER, EMANUEL: A rapid bedside test for measuring sedimentation rate, New York State Jr. Med., 1939, xxxix, 867-869.
325. GOLDFAIN, E.: Gastro-intestinal therapy in atrophic arthritis, Arch. Phys. Therap., 1939, xx, 357-360.
326. GOLDIE, WILLIAM: The effect of chrysotherapy on the sedimentation rate in rheumatoid arthritis, Ann. Rheumat. Dis., 1939, i, 319-332.
327. GORDON, M. H.: Experimental fibrositis due to a virus, and some observations on the experimental production of arthritis, Rheumat. Dis., 1939, i, 5-14.
328. GORDON, R. C.: The psychological factor in chronic rheumatism, Brit. Med. Jr., 1939, i, 1165-1169.
329. GORNITSKAYA, F. A.: Evolution of cardiac lesions in juvenile rheumatic infection, Acta rheumatol., 1938, x, 6-7.
330. GORRELL, R. L.: The nupercaine treatment of lumbago, Tri-State Med. Jr., 1939, xi, 2223-2224.
331. GOTTESMAN, SAMUEL: Combined technique of hot box and ultrashort wave for local and general fever, Med. Rec., 1939, cl, 365-367.
332. GRABFIELD, G. P.: Clinical possibilities in the study of the renal innervation, Internat. Clin., 1939, s. 2. i, 93-97.

333. GRABFIELD, G. P.: The effect of certain polyhydric alcohols and sugars on purine excretion, *Trans. Assoc. Am. Physicians*, 1939, liv, 91-93.
334. GRABFIELD, G. P., and SWANSON, D.: Studies on the denervated kidney. V. The effects of unilateral denervation in acute experiments on the uricosuric effect of cinchophen, *Jr. Pharmacol. and Exper. Therap.*, 1939, lxvi, 60-65.
335. GREEN, A. G.: The pharmacology of aspirin and its calcium salt, *Rheumatism*, 1939, i, 25-29 (Oct.).
336. GREEN, C. A.: Researches into the aetiology of acute rheumatism; I.—Rheumatic carditis: Post-mortem investigation of nine consecutive cases, *Ann. Rheumat. Dis.*, 1939, i, 86-98.
337. GREEN, C. A.: Some observations on possible streptococcal aetiology of acute rheumatism, *Jr. Roy. Nav. Med. Serv.*, 1939, xxv, 218-232.
338. GREEN, C. A., THOMSON, S., and GLAZEBROOK, A. J.: The formol-gel reaction and erythrocyte sedimentation rate in acute rheumatism, *Ann. Rheumat. Dis.*, 1939, i, 180-195.
339. GREEN, C. C., and GONDY, J. R.: Treatment of sciatic syndrome by iliotibial fascial band section, *Ann. Surg.*, 1939, cix, 1024-1026.
340. GREEN, W. T.: Orthopedic considerations in the treatment of arthritis, *Am. Jr. Surg.*, 1939, n.s. xliv, 201-217.
341. GREGG, DONALD: The relative immunity of psychotic cases to arthritis, angina pectoris and other diseases; an explanatory thesis, *Trans. Am. Neurol. Assoc.*, 1938, lxiv, 151-156.
342. GREGG, DONALD: The paucity of arthritis among psychotic cases, *Am. Jr. Psychiat.*, 1939, xcv, 853-858.
343. GREGG, R. O.: Effect of anemia on sedimentation rate, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 600-605.
344. GUPTA, N. R.: Modern treatment of gonorrhoea and its complications in the male, *Calcutta Med. Jr.*, 1939, xxxv, 461-466.
345. GUY, W. H., GRAUER, R. C., and JACOB, F. M.: Poikilodermatomyositis, *Arch. Dermat. and Syph.*, 1939, xl, 867-875.
346. GUYER, M. F., and CLAUS, P. E.: Irradiation of cancer following injection of colchicine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 565-568.
347. GWYNN, H. B.: Treatment of arthritis by artificial fever therapy, *Rheumatism*, 1939, i, 17-24 (Jan.).
348. VON HAAM, E., and FROST, T. T.: Changes in the parenchymatous organs produced by artificially induced fever, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 99-103.
349. HADLEY, L. A.: Anatomicroradiographic studies of the spine; changes responsible for certain painful back conditions, *New York State Jr. Med.*, 1939, xxxix, 969-974.
350. HALL, A. S.: Erythema nodosum, *Lancet*, 1939, i, 572.
351. HALL, B. E.: Influence of sulfanilamide on blood, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 155-157.
352. HALL, C. L.: Hyperparathyroidism and osteitis fibrosa cystica, *Am. Jr. Surg.*, 1939, n.s. xliii, 585-593.
353. HALL, M. G., DARLING, R. C., and TAYLOR, F. H. L.: The vitamin C requirement in rheumatoid arthritis, *ANN. INT. MED.*, 1939, xiii, 415-423.
354. HALL, M. G., SANDERSON, ROBERT, and FELDMAN, THEODORE: A clinical chart for chronic arthritis, *New England Jr. Med.*, 1938, ccxix, 985-987.
355. HALLOCK, HALFORD: Reconstructive and stabilizing surgery; for residual suppurative arthritis of hip joint; a study of forty-six unselected cases, *Jr. Am. Med. Assoc.*, 1939, cxliii, 2398-2404.
356. HAM, T. H., and CURTIS, FANNY C.: Sedimentation rate of erythrocytes; influence of technical, erythrocyte and plasma factors and quantitative comparison of five commonly used sedimentation methods, *Medicine*, 1938, xvii, 447-517.

357. HAMANN, E. E., and HUDDLESON, I. F.: Effect of sulfapyridine (dagenan) on *Brucella abortus* in vitro and in vivo, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 555-556.
358. HAMBLEN-THOMAS, C.: Nasal catarrh and nasal sinusitis in their relation to chronic rheumatism, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 11-15.
359. HAMBLEN-THOMAS, C.: Throat affections and rheumatic diseases, *Brit. Jr. Rheumat.*, 1939, i, 189-192.
360. HAMBLETON, A., and CHRISTIANSON, R. A.: The choice of technique for the sedimentation test, *Am. Jr. Med. Sci.*, 1939, cxcviii, 177-187.
361. HAMILTON, A. S.: Air injection (pneumarthrography) as an aid in the diagnosis of industrial and athletic injuries of the knee joint, *South. Med. Jr.*, 1939, xxxii, 533-539.
362. HAMLIN, EDWARD, JR., and SARRIS, S. P.: Acute gonococcal tenosynovitis; report of seven cases, *New England Jr. Med.*, 1939, ccxxi, 228-231.
363. HANSEN, A. E.: Rheumatic fever in children; evidences of activity of the infection and notes on various therapeutic procedures, *Journal-Lancet*, 1939, lix, 201-206.
364. HARDGROVE, MAURICE: Guiding the cardiac child, *Milwaukee Med. Times*, 1939, xii, 19-20.
365. HARRIS, A. W., LYNCH, G. W., and O'HARE, J. P.: Periarthritis nodosa, *Arch. Int. Med.*, 1939, lxiii, 1163-1182.
366. HARRIS, R. I., and COULTHARD, H. S.: Multiple pathological fractures caused by tuberculosis, *Canad. Med. Assoc. Jr.*, 1939, xli, 434-436.
367. HARRIS, WILFRED: Sciatica and its treatment, *Brit. Med. Jr.*, 1938, ii, 1245-1247.
368. HART, F. D.: Rheumatic subcutaneous nodule formation, *Ann. Rheumat. Dis.*, 1939, i, 196-200.
369. HARTSOCK, C. L.: Headache caused by arthritis of the cervical spine, *Cleveland Clin. Quart.*, 1939, vi, 261-264.
370. HASTINGS, R. E.: Low back pain with sciatic radiation, *Southwestern Med.*, 1939, xxiii, 183-185.
371. HAVAS, LÁSZLÓ: Colchicine and colchicine effects, *Chem. Products*, 1939 (July).
372. HAWKSLEY, J. C.: The nature of growing pains and their relation to rheumatism in children and adolescents, *Brit. Med. Jr.*, 1939, i, 155-157.
373. HEDLEY, O. F.: Rheumatic heart disease—a national health problem, *Proc. Assoc. Life Insur. Med. Dir. America* (1938), 1939, xxv, 163-201.
374. HEDLEY, O. F.: Trends, geographical and racial distribution of mortality from heart disease among persons 5-24 years of age in the United States during recent years (1922-1936); a preliminary report, *Pub. Health Rep.*, 1939, liv, 2271-2297.
375. HEMINGWAY, ALLAN: Physical and biological aspects of short wave diathermy, *Arch. Phys. Therap.*, 1939, xx, 24-28.
376. HENCH, P. S.: Recent researches on arthritis and rheumatism in the United States, *Ann. Rheumat. Dis.*, 1939, i, 109-133.
377. HENCH, P. S.: The advantages of hepatic injury and jaundice in certain conditions, notably the rheumatic diseases, *Med. Clin. N. Am.*, 1940, xxiv, 1209-1237.
378. HENDERSON, M. S.: Discussion, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 233-234.
379. HENDRY, A. W., and ANDERSON, T. E.: Dermatomyositis, *Lancet*, 1939, i, 80-82.
380. HERNAMAN-JOHNSON, F.: What's in a name, *Rheumatism*, 1938, i, 96-99 (Oct.).
381. HERRMAN, W. G.: Value of roentgen therapy in acute subacromial bursitis, *Jr. Med. Soc. New Jersey*, 1939, xxxvi, 529-532.
382. HEWINS, W. W.: The treatment and management of gonorrhea, *Jr. Indiana Med. Assoc.*, 1939, xxxii, 69-71.
383. HEYMAN, C. H.: An orthopedic surgeon looks at the American Physiotherapy Association, *Physiotherapy Rev.*, 1939, xix, 90-92.
384. HEYMAN, C. H.: Posterior fasciotomy in the treatment of back pain, *Jr. Bone and Joint Surg.*, 1939, xxi, 397-404.

385. HICKS, R. A., and WYATT, B. L.: Leucopenic index in relation to chronic arthritis, *Southwestern Med.*, 1938, xxii, 480-483.
386. HIGGINS, W. H.: Current trends in the treatment of chronic arthritis, *Virginia Med. Monthly*, 1939, lxvi, 269-275.
387. HILL, LEONARD: Rheumatism and climate, *Brit. Med. Jr.*, 1939, ii, 276-278.
388. HILL, LEONARD, and TAYLOR, H. J.: Physical treatment of rheumatic disease, *Lancet*, 1939, ii, 351-352; *Brit. Med. Jr.*, 1939, ii, 341.
389. HIRSCH, E. F., and MORGAN, R. H.: Causal significance to traumatic ossification of the fibrocartilage in tendon insertions, *Arch. Surg.*, 1939, xxxix, 824-837.
390. HOLLANDER, J. L.: The diagnosis and treatment of gout, *Med. Clin. N. Am.*, 1939, xxiii, 1437-1448.
391. HOLLAR, E. D., and AGNOR, E. B.: Hypertrophic pulmonary osteo-arthropathy; report of case, *Jr. Med. Assoc. Georgia*, 1939, xxviii, 63-64.
392. HOLMBLAD, E. C.: Improved x-ray technic in studying knee joints, *South. Med. Jr.*, 1939, xxxii, 240-243.
393. HOLMES, GEOFFREY: The immersion bath, *Harrogate Spa Med. Jr.*, 1938, i, 3-7.
394. HOPKINS, F. S., and HUSTON, L. L.: Knee injuries in athletics; a study of end results, *New England Jr. Med.*, 1939, ccxxi, 95-102.
395. HOPKINS, H. H., and ZUCK, F. N.: Arthroplasty of hip, with use of vitallium cup, *Med. Bull. Vet. Admin.*, 1938, xv, 1-2.
396. HOPKINS, H. H., and ZUCK, F. N.: Arthroplasty of the hip with use of vitallium cup (supplemental report), *Med. Bull. Vet. Admin.*, 1939, xv, 217.
397. HORDER, —.: Empire Rheumatism Council—Second annual report, *Rheumat. Dis.*, 1939, i, 57-62; *Brit. Jr. Rheumat.*, 1939, i, 151-155.
398. HORWITZ, M. T.: Injuries of the ligaments of the knee joint; an experimental study, *Arch. Surg.*, 1939, xxxviii, 946-954.
399. HORWITZ, M. T.: Lesions of the supraspinatus tendon and associated structures; investigation of comparable lesions in hip joint, *Arch. Surg.*, 1939, xxxviii, 990-1003.
400. HORWITZ, THOMAS: Lesions of the intervertebral disk and ligamentum flavum of the lumbar vertebrae. An anatomic study of 75 human cadavers, *Surgery*, 1939, vi, 410-425.
401. HOSPITAL SERVICE: Approved schools of occupational therapy, *Jr. Am. Med. Assoc.*, 1939, cxii, 926-927.
402. HOSPITAL SERVICE: Essentials of an acceptable school for physical therapy technicians, *Jr. Am. Med. Assoc.*, 1939, cxii, 927.
403. HOSPITAL SERVICE: Schools for physical therapy technicians, *Jr. Am. Med. Assoc.*, 1939, cxii, 928-929.
404. HOWARD, C. R. G.: Epidemic myalgia; five cases in one household, *Brit. Med. Jr.*, 1938, ii, 1203-1204.
405. HOWARD, M. W.: Gonorrhea and its complications, *Kentucky Med. Jr.*, 1939, xxxvii, 278-280.
406. HOWARD, N. J.: Subcutaneous dorsal digital bursitis, *Surgery*, 1939, v, 939-941.
407. HOWARD, N. J.: Acromioclavicular and sternoclavicular joint injuries, *Am. Jr. Surg.*, 1939, n.s. xlvii, 284-291.
408. HOWELL, B. W.: The surgical treatment of arthritis, Rheumatism, 1938, i, 17-24 (July).
409. HOWELL, W. H.: Hemophilia; Wesley M. Carpenter lecture, *Bull. New York Acad. Med.*, 1939, xv, 3-26.
410. HOWITT, F. D.: The diagnosis and treatment of chronic articular rheumatism, *Practitioner*, 1939, cxliii, 246-262.
411. HUBBARD, J. P., and MCKEE, MARGARET H.: The anemia of rheumatic fever, *Jr. Pediat.*, 1939, xiv, 66-73.
412. HUDSON, O. C.: Intractable abdominal pain associated with backache, *Med. Times*, New York, 1939, lxvii, 514-515.

413. HUDSON, O. C., and HETTESHEIMER, C. A.: Causalgia; a cause of backache, *Med. Times*, New York, 1939, lxxvii, 211-214.
414. HUMMON, I. F., JR.: Manipulation in low back cases, *Arch. Phys. Therap.*, 1939, xx, 224-226.
415. HUNT, THOMAS: Indigestion and rheumatism, *Rheumatism*, 1938, i, 88-90 (Oct.).
416. HURT, SUE: Occupational therapy with traumatic conditions, *Occup. Therap.*, 1939, xviii, 191-194.
417. ILFELD, F. W.: A new method of strapping for back strain with sciatica, *New England Jr. Med.*, 1939, ccxx, 412-415.
418. INRIE, A. H., and AITKENHEAD, ANNE C.: Amyloidosis complicating Still's disease, *Lancet*, 1939, ii, 421-422.
419. IRISH, W. H., and STUMP, J. P.: Villous synovitis of the knees due to improper weight distribution, *Arch. Phys. Therap.*, 1939, xx, 391-396; 405.
420. IRWIG, FRED: Treatment of low back pain; observations as to the more common origin of "sacro-iliac disease," *Indust. Med.*, 1939, viii, 105-112.
421. ISHMAEL, W. K.: The use of autohemotherapy reinforced with artificial fever in the treatment of rheumatic disease, *Jr. Oklahoma Med. Assoc.*, 1939, xxxii, 337-343.
422. JACOX, H. W., KING, J. M., and BAILEY, F. R.: Parathyroidism; effect of irradiation of the neck on the repair of bone lesions, *Am. Jr. Roentgenol.*, 1939, xli, 970-978.
423. JAFFE, H. L.: Bone rarefaction after trauma to large joint regions without fracture, *Radiology*, 1939, xxxiii, 305-311.
424. JOHNSON, A. S.: The present status of the blood sedimentation rate, *New England Jr. Med.*, 1939, ccxx, 823-827.
425. JOHNSON, H. F., and WHISTON, GORDON: The orthopaedic care of the arthritic patient, *Nebraska Med. Jr.*, 1939, xxiv, 289-293.
426. JOHNSON, J. B., and ANSPACH, H. M.: Early roentgenologic signs in some of the more common disorders of the hip, *South. Med. Jr.*, 1939, xxxii, 1228-1235.
427. JONES, D. E.: Backache, *Kentucky Med. Jr.*, 1939, xxxvii, 64-70.
428. JONES, H. W. E., and TAYLOR, STEPHEN: Vitamins in the treatment of rheumatism in children, *St. Thomas's Hosp. Rep.*, 1938, iii, 114-118.
429. JONES, T. D., and MOTE, J. R.: The clinical importance of infection of the respiratory tract in rheumatic fever, *Jr. Am. Med. Assoc.*, 1939, cxiii, 898-902.
430. JORDAN, H. H.: The role of posture in chronic arthritis, *New York State Jr. Med.*, 1939, xxxix, 1823-1831.
431. JOSE, GILBERT: Experiences in the treatment of urethritis by sulphanilamide, *Med. Jr. Australia*, 1939, i, 54-56.
432. JOSTES, F. A.: Backache: a manipulative treatment without anaesthesia, *Med. Press*, 1939, ccii, 132-139.
433. JOSTES, F. A., and ROCHE, M. B.: Syphilis of the bones and joints, *Jr. Missouri Med. Assoc.*, 1939, xxxvi, 61-68.
434. JUDOVICH, B. D., and BATES, WILLIAM: Low back pain; a study of over 1000 cases, *Indust. Med.*, 1939, viii, 160-165.
435. JULER, FRANK: On iritis and cyclitis, *Rheumatism*, 1939, i, 16-25 (April).
436. JUSTER, I. R.: The significance of rheumatic activity in chronic rheumatic heart disease, *Am. Heart Jr.*, 1939, xvii, 669-680.
437. KAHLSTROM, S. C., BURTON, C. C., and PHEMISTER, D. B.: Aseptic necrosis of bone. I. Infarction of bones in caisson disease resulting in encapsulated and calcified areas in diaphyses and in arthritis deformans, *Surg., Gynec. and Obst.*, 1939, lxxviii, 129-146.
438. KAHLSTROM, S. C., BURTON, C. C., and PHEMISTER, D. B.: Aseptic necrosis of bone. II. Infarction of bones of undetermined etiology resulting in encapsulated and calcified areas in diaphyses and in arthritis deformans, *Surg., Gynec. and Obst.*, 1939, lxxviii, 631-641.
439. KARK, WILFRED: Spondylolisthesis, *Brit. Jr. Surg.*, 1939, xxvii, 149-150.

440. KAUFMAN, J. G.: The management of the rheumatic patient, Jr. Med. Soc. New Jersey, 1939, xxxvi, 496-500.
441. KEEFER, C. S.: Sulfanilamide and sulfapyridin in the treatment of various infections, California and West. Med., 1939, li, 81-84.
442. KEEFER, C. S.: Sulfanilamide: its mode of action and side effects, Med. Clin. N. Am., 1939, xxiii, 1133-1148.
443. KEEFER, C. S., and RANTZ, L. A.: Sulphanilamide in the treatment of gonococcal arthritis, Am. Jr. Med. Sci., 1939, cxcvii, 168-181.
444. KEIL, HARRY: A note on Edward Jenner's lost manuscript on "Rheumatism of the heart," Bull. Inst. Hist. Med., 1939, vii, 409-411.
445. KELLOGG, FREDERICK, and CUNHA, FELIX: Dermatomyositis; report of case associated with rheumatic heart disease, California and West. Med., 1939, 1, 337-339.
446. KERNOHAN, J. W., WOLTMAN, H. W., and BARNES, A. R.: Involvement of the nervous system associated with endocarditis; neuropsychiatric and neuropathologic observations in forty-two cases of fatal outcome, Arch. Neurol. and Psychiat., 1939, xlii, 789-809.
447. KERSLEY, G. D.: Spondylitis and its treatment, Med. World, 1939, 1-4.
448. KERSLEY, G. D.: Subacute rheumatic infection, Jr. Roy. Inst. Pub. Health and Hyg., 1939, ii, 101-103.
449. KERSLEY, G. D.: Gout, Brit. Jr. Rheumat., 1939, ii, 22-26.
450. KETRON, L. W., and BERNSTEIN, J. C.: Cutaneous manifestations of periarteritis nodosa, Arch. Dermat. and Syph., 1939, xl, 929-944.
451. KEY, J. A.: Discussion (Abstr.), Jr. Am. Med. Assoc., 1939, cxiii, 2404-2405.
452. KEY, J. A., ROSENFELD, HERMAN, and TJOFLAT, O. E.: Gold therapy in proliferative (especially atrophic) arthritis, Jr. Bone and Joint Surg., 1939, xxi, 339-345.
453. KIEL, O. B.: Acetyl beta methylcholine chloride by iontophoresis in the treatment of arthritis and certain peripheral vascular disturbances of the extremities, Texas State Jr. Med., 1938, xxxiv, 530-534.
454. KING, M. K.: Sciatic neuritis and low back pain caused by rupture of the intervertebral discs, Virginia Med. Monthly, 1939, lxvi, 656-659.
455. KIRSTEIN, M. B., and BROMBERG, LEON: The effect of fever therapy upon carbohydrate metabolism, Jr. Lab. and Clin. Med., 1939, xxv, 7-10.
456. KLEEBOEG, J., GUREVITCH, I., and ALKAN, W. J.: Sulphanilamide therapy in undulant fever and a new method of blood culture, Trans. Roy. Soc. Trop. Med. and Hyg., 1939, xxxiii, 183-189.
457. KLEINBERG, SAMUEL: Backache, Med. Rec., 1939, cxlix, 5-9.
458. KLEINBERG, SAMUEL: Traumatic myositis ossificans; report of a case following fracture at the elbow, Ann. Surg., 1939, cx, 144-148.
459. KLEINBERG, SAMUEL: The industrial low back from the orthopedic standpoint, New York State Jr. Med., 1939, xxxix, 1725-1734.
460. KLEINBERG, SAMUEL: Low back pain and sciatica secondary to a strain in a prespondylolisthesis of the fourth and fifth lumbar vertebrae, Am. Jr. Surg., 1939, xlv, 584-586.
461. KLING, D. H.: The significance of peripheral circulatory disturbances for the development of osteo-arthritis, Am. Jr. Med. Sci., 1939, cxcvii, 358-369.
462. KLING, D. H.: A histamine ointment for cataphoresis and inunction in rheumatic affections and diseases of the peripheral circulation, Med. Rec., 1939, cl, 291.
463. KLING, D. H., SASHIN, DAVID, and SPANBOCK, JOSEPH: The mechanism of gold therapy in rheumatoid arthritis, Jr. Lab. and Clin. Med., 1939, xxiv, 1241-1245.
464. KOLETSKY, SIMON: Fatal hemolytic anemia following the administration of sulfanilamide, Jr. Am. Med. Assoc., 1939, cxiii, 291-294.
465. KOLMER, J. A., and BONDI, AMEDEO: Studies in active immunization against undulant fever; I. Antibody production by rabbits immunized with heat-killed Brucella abortus

- alone and simultaneously with heat-killed *Bacillus typhosus*, Jr. *Immunol.*, 1939, xxxvii, 489-506.
466. KOPP, ISRAEL: Technic, physiology and results in the application of therapeutic hyperpyrexia, Jr. *Connecticut Med. Soc.*, 1939, iii, 68-74.
467. KOPPE, H. F.: Hyperparathyroidism, *Ohio State Med. Jr.*, 1939, xxxv, 257-260.
468. KOVACS, RICHARD: Uses and misuses of therapeutic apparatus, *Med. Rec.*, 1939, cxlix, 297-299.
469. KOVÁCS, RICHARD: Present status of short wave diathermy, *Arch. Phys. Therap.*, 1939, xx, 559-566.
470. KRUSEN, F. H.: Physical therapy in arthritis, *New England Jr. Med.*, 1939, ccxx, 463-467.
471. KRUSEN, F. H.: Recent developments in physical therapy, *Physiotherapy Rev.*, 1939, xix, 316-320.
472. KRUSEN, F. H., and BASOM, W. C.: Easily overlooked conditions of the back and shoulder girdle: their relation to physical therapy, *Minnesota Med.*, 1939, xxii, 746-750.
473. KRUSEN, F. H., and ELKINS, E. C.: Investigations in fever therapy, *Arch. Phys. Therap.*, 1939, xx, 77-84; 110
474. KRUSEN, F. H., and ELKINS, E. C.: Council on Physical Therapy; fever therapy by physical means, Jr. *Am. Med. Assoc.*, 1939, cxii, 1689-1696.
475. KRUSEN, F. H., and ELKINS, E. C.: Clinical results of fever therapy, *Arch. Phys. Therap.*, 1939, xx, 346-353; 376.
476. KUHNS, J. G.: Care of the foot in chronic arthritis, *Rheumatism*, 1939, i, 6-17 (Jan.).
477. KUTTNER, ANN G., and REYERSBACH, GERTRUDE: The value of special radiologic procedures in detecting cardiac enlargement in children with rheumatic heart disease, *Am. Heart Jr.*, 1939, xviii, 213-227.
478. LECOCQ, J. F.: Diagnosis and treatment of bone and joint tuberculosis, *Northwest. Med.*, 1939, xxxviii, 349-352.
479. LEDBETTER, A. A.: Artificial fever therapy in a private hospital, *Texas State Jr. Med.*, 1939, xxxiv, 753-757.
480. LEE, H. M.: Protruded intervertebral disc: case report, *Minnesota Med.*, 1939, xxii, 506-507.
481. LESLIE, C. J.: The role of the preventive health examination in the diagnosis of rheumatic heart disease, *Proc. Life Extension Examiners*, 1939, i, 99-104.
482. LESSER, HENRY: Social and industrial aspects of rheumatism, *Brit. Jr. Rheumat.*, 1939, ii, 111-116.
483. LEVINTHAL, WALTER: The aetiological problem of rheumatism, *Ann. Rheumat. Dis.*, 1939, i, 67-85.
484. LEWIS, M. D., and GUNDERSON, M. F.: The effect of artificial fever on the blood sulfanilamide level in rabbits, *Arch. Phys. Therap.*, 1939, xx, 432-436.
485. LEWIS, R. A.: Rheumatic heart disease, *Ohio State Med. Jr.*, 1939, xxxv, 398-400.
486. LICHTENSTEIN, LOUIS: Pathological changes following therapeutic hyperthermia. Report of a case, *Am. Jr. Path.*, 1939, xv, 363-376.
487. LICHTMAN, S. S.: Toxic hepatitis ascribed to the use of cinchophen. Illustration of the analgesic effect of jaundice in long-standing rheumatoid arthritis, *Jr. Mt. Sinai Hosp.*, 1939, vi, 199-202. Also *personal communication to the Authors*.
488. LINDBLOM, KNUT: The arthrographic appearance of the ligaments of the knee joint, *Acta Radiol.*, 1938, xix, 582-600.
489. LITTLE, NORMAN: The differential diagnosis of internal derangement of the knee joint, *Med. Jr. Australia*, 1939, i, 895-900.
490. LIVINGSTON, A. E., GRAY, H. D., and DECKER, H. G.: A case of undulant fever treated with sulfanilamide, *Jr. Iowa Med. Soc.*, 1939, xxix, 156-157.
491. LLOYD, V. E., AND OTHERS: Discussion on sulphonamide therapy in gonorrhoea, *Brit. Jr. Ven. Dis.*, 1939, xv, 100-140.

492. LOCKE, ARTHUR, MAIN, E. R., and MELLON, R. R.: Non-specific factors in resistance: III. Capacity for retarding bacterial proliferation, *Jr. Immunol.*, 1939, xxxvi, 183-192.
493. LOCKIE, L. M.: A discussion of a therapeutic test and a provocative test in gouty arthritis, *ANN. INT. MED.*, 1939, xiii, 755-760.
494. LOGUE, J. B.: Incision of fascia lata for relief of low back pain with sciatica with case reports, *U. S. Nav. Med. Bull.*, 1939, xxxvii, 541-546.
495. LONG, P. H.: Sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 538-539.
496. LONG, P. H.: Sulfanilamide and its derivatives; the nurse's responsibility toward the patient who is receiving sulfanilamide or its derivatives, *Am. Jr. Nursing*, 1939, xxxix, 719-727.
497. LONG, P. H., BLISS, ELEANOR A., and FEINSTONE, W. H.: Mode of action, clinical use and toxic manifestations of sulfanilamide, *Jr. Am. Med. Assoc.*, 1939, cxii, 115-121.
498. LONG, P. H., HAVILAND, J. W., EDWARDS, LYDIA B., and BLISS, ELEANOR A.: The toxic manifestations of sulfanilamide and its derivatives with reference to their importance in the course of therapy, *Jr. Am. Med. Assoc.*, 1940, cxv, 364-368.
499. LOVE, J. G.: Low back and sciatic pain, *Surg. Clin. N. Am.*, 1939, xix, 943-953.
500. LOVE, J. G.: Protruded intervertebral disc (fibrocartilage), *Proc. Roy. Soc. Med.*, 1939, xxxii, 1697-1712.
501. LOVE, J. G.: Protruded intervertebral disks with a note regarding hypertrophy of ligamenta flava, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2029-2034.
502. LUBOWE, I. I.: The relationship of physiotherapy to the practice of medicine, *Med. Rec.*, 1939, cxlix, 183-185.
503. LUNDY, C. J.: The prevention and early diagnosis of rheumatic heart disease, *Nebraska Med. Jr.*, 1939, xxiv, 83-86.
504. LYNCH, J. P.: The erythrocyte sedimentation phenomenon—a review, *Virginia Med. Monthly*, 1939, lxvi, 409-412.
505. MACDONALD, H. K.: Inflammation. Bursitis, *Canad. Med. Assoc. Jr.*, 1939, xl, 573-577.
506. MACEY, H. B.: A new operative procedure for repair of ruptured cruciate ligaments of the knee joint, *Surg., Gynec. and Obst.*, 1939, lxix, 108-109.
507. MACEY, H. B.: Backache resulting from changes in the interspinal ligaments; preliminary report, *Proc. Staff. Meet. Mayo Clin.*, 1939, xiv, 425-426.
508. MACKENNA, F. S.: The use of bee venom in rheumatism, *Med. Press*, 1939, cci, 386-390.
509. MACLEOD, C. M.: Chemotherapy of pneumococcic pneumonia, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1405-1410.
510. MADDEN, J. F.: Cholesterol balance and low fat diet in psoriasis, *Arch. Dermat. and Syph.*, 1939, xxxix, 268-276.
511. MADDEN, J. F.: Psoriasis; a clinical and laboratory statistical study, *Minnesota Med.*, 1939, xxii, 381-385.
512. MAGNUSON, P. B.: Arthritis and injury—and their relation to injury and arthritis, *Indust. Med.*, 1939, viii, 231-234.
513. MAISON, G. L.: Studies of the genesis of ischemic pain; the influence of the potassium, lactate and ammonium ions, *Am. Jr. Physiol.*, 1939, cxxvii, 315-321.
514. MAKAROFF, W. N.: The etiology of lumbago and sciatica, *Indust. Med.*, 1939, viii, 1-4.
515. MALCOLM, MABEL M., and DOLMAN, C. E.: Gonococcus culturing in public health laboratory practice, *Canad. Pub. Health Jr.*, 1939, xxx, 252-259.
516. MARCUS, N. L.: Agranulocytosis and sulfanilamide, *Jr. Florida Med. Assoc.*, 1939, xxv, 489-496.
517. MARSHALL, E. K., JR.: Bacterial chemotherapy; the pharmacology of sulfanilamide, *Physiol. Rev.*, 1939, xix, 240-269.
518. MASSIE, EDWARD, and LEVINE, S. A.: The prognosis and subsequent developments in acute rheumatic pericarditis, *Jr. Am. Med. Assoc.*, 1939, cxii, 1219-1223.
519. MAYERS, L. H., and LIVINGSTON, S. K.: The treatment of arthritis and associated conditions; a preliminary report, *Indust. Med.*, 1939, viii, 3-20.

520. McCARTIE, D. B.: Rheumatic fever, *Med. Rec.*, 1939, cl, 43-47; 85-87.
521. McCAULEY, J. C., JR.: Arthrodesis in Charcot's knees, *New York State Jr. Med.*, 1939, xxxix, 2132-2137.
522. McDONALD, J. E., and STUART, F. A.: Stenosing tendovaginitis at the radial styloid process, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 1035.
523. McGINTY, A. P., and GAMBRELL, W. ELIZABETH: Chronic brucellosis, *Internat. Clin.*, 1939, i, 1-27.
524. MCGOVERN, F. H.: Otogenic acute suppurative arthritis, *Virginia Med. Monthly*, 1939, lxvi, 146-148.
525. McILHENNY, P. A.: Subdeltoid bursitis, *New Orleans Med. and Surg. Jr.*, 1939, xci, 403-407.
526. McKAY, W. J. S.: Allergy-gout, *Med. Press*, 1939, cci, 528-532; 546-549; 570-574.
527. McKEE, C. M., RAKE, GEOFFREY, GREEP, R. O., and VAN DYKE, H. B.: Therapeutic effect of sulfathiazole and sulfapyridine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 417-421.
528. McKEEVER, F. M.: Tuberculosis of the knee in infancy and childhood, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1293-1299.
529. McMURRAY, T. P.: Osteo-arthritis of the hip joint, *Jr. Bone and Joint Surg.*, 1939, xxi, 1-11.
530. MENEFEE, E. E., JR., and POSTON, MARY A.: Effects of sulfanilamide on *Brucella melitensis*, var. *melitensis*, *abortus*, and *suis*, *Jr. Bact.*, 1939, xxxvii, 269-276.
531. MENEFEE, E. E., JR., and POSTON, MARY A.: Significance of standard laboratory procedures in the diagnosis of brucellosis, *Am. Jr. Med. Sci.*, 1939, cxcvii, 646-653.
532. MENNELL, JAMES: Physical treatment and the rheumatic knee, *Brit. Jr. Rheumat.*, 1939, i, 220-229.
533. MENNELL, JAMES: The value of manipulation in the treatment of rheumatic diseases, *Post-Grad. Med. Jr.*, 1939, n.s. xv, 301-308.
534. MERRITT, E. A.: Radiation control of hyperparathyroidism, *Jr. Iowa Med. Soc.*, 1939, xxix, 373-377.
535. MESSELOFF, C. R.: Observations on the use of quinidine sulfate in children, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 574-580.
536. MEYER, KARL, SMYTH, ELIZABETH M., and DAWSON, M. H.: The isolation of a mucopolysaccharide from synovial fluid, *Jr. Biol. Chem.*, 1939, cxxviii, 319-327.
537. MEYER, OTTO: Latent phlebitis as a cause of rheumatism, *Rheumatism*, 1939, i, 24-31 (Jan.).
538. MILLER, E. R.: Carcinoma of the thymus, with marked pulmonary osteo-arthropathy, *Radiology*, 1939, xxxii, 651-660.
539. MILLER, SINCLAIR, and WILSON, J. V.: Nutrition and diet in rheumatism, *Med. Press*, 1939, cci, 390-393; 411-413.
540. MITCHINER, P. H.: Penetrating wounds of joints, *St. Thomas's Hosp. Gaz.*, 1939, xxxvii, 182-186.
541. MITCHINER, P. H., and COWELL, E. M.: The air-raid: VII. Wounds of bones and joints, *Lancet*, 1939, i, 408-411.
542. MONROE, R. T.: Chronic arthritis. In: *Oxford Loose-Leaf Medicine*, New York, The Oxford University Press, 1939, chap. xv, pp. 367-404.
543. MONTGOMERY, D. W.: The knee, *Ann. Med. Hist.*, 1939, i, 388-395.
544. MONTGOMERY, HAMILTON: Pathology of lupus erythematosus, *Jr. Invest. Dermat.*, 1939, ii, 343-359.
545. MORRISON, SAMUEL: Gastro-intestinal aspects of backache, *Internat. Med. Digest*, 1939, xxxiv, 249-251.
546. MORTON, A. P.: Laminectomy for low back pain with case reports. *U. S. Nav. Med. Bull.*, 1939, xxxvii, 523-538.

547. MOSCHCOWITZ, ELI: The nosological status of periarteritis nodosa, *Jr. Mt. Sinai Hosp.*, 1938, v, 337-339.
548. MOSELEY, H. F.: Rupture of the supraspinatus tendon, *Canad. Med. Assoc. Jr.*, 1939, xli, 280-282.
549. MUETHER, R. O., and ANDREWS, K. R.: Combined use of typhoid vaccine and neoprontosil in treatment of gonococcal arthritis, *Jr. Missouri Med. Assoc.*, 1939, xxxvi, 383-387.
550. MUMFORD, E. B., and REYNOLDS, F. C.: The injured back, *Jr. Indiana Med. Assoc.*, 1939, xxxii, 358-362.
551. MUNGER, MYRTLE, and HUDDLESON, I. F.: A preliminary report of the blood picture in brucellosis, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 617-619.
552. MURPHY, F. G.: Osteochondritis dissecans of the elbow joint, *Jr. Bone and Joint Surg.*, 1939, xxi, 464-466.
553. MURRAY, J. M.: Lower back pain, *Canad. Med. Assoc. Jr.*, 1939, xli, 427-434.
554. NAIR, V. G., and CHETTY, V. V.: Chemotherapy and lymphogranuloma inguinale, *Indian Jr. Ven. Dis.*, 1939, v, 28-33.
555. NELIGAN, A. R.: The diagnosis and treatment of fibrositis and neuritis, *Practitioner*, 1939, cxliii, 263-274.
556. NETER, ERWIN: Action of sulfanilamide on hemolytic enterococcus (*Streptococcus fecalis hemolyticus*), *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 668-672.
557. NEWCOMER, N. B.: The joint changes in hemophilia, *Radiology*, 1939, xxxii, 573-582.
558. NEYMANN, C. A.: Historical development of artificial fever in the treatment of disease, *Med. Rec.*, 1939, cl, 89-92.
559. NEYMANN, C. A., and OSBORNE, S. L.: The dangers of electropyrexia, *Med. Rec.*, 1939, cl, 423-426.
560. NICHOLS, R. E.: A new instrument for automatically recording the erythrocyte sedimentation rate and the volume percentage of cells and plasma upon a single permanent record, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 631-635.
561. NICHOLSON, J. T.: Knee injuries, *Surg. Clin. N. Am.*, 1938, xviii, 1671-1693.
562. NICOL, HAMISH, and FREEDMAN, BERNARD: Fatal agranulocytosis following treatment with M. & B. 693, *Lancet*, 1939, ii, 647-648.
563. NISSEN, H. A., and SPENER, K. A.: A follow-up study of three "rheumatic" patients *Brit. Jr. Rheumat.*, 1939, i, 156-173.
564. NORBURY, F. G.: Gonorrheal myelitis with associated porphyrinuria following sulfanilamide, *Jr. Lab. and Clin. Med.*, 1939, xxv, 270-274.
565. NUNNEMACHER, R. F.: Experimental studies on the cartilage plates in the long bones of the rat, *Am. Jr. Anat.*, 1939, lxxv, 253-289.
566. NUTTER, J. A.: Fasciotomy for chronic sciatica and backache: an analysis of end-results, *Canad. Med. Assoc. Jr.*, 1939, xl, 571-573.
567. OBER, F. R.: Discoid cartilage, trigger knee, *Surgery*, 1939, vi, 24-30.
568. OCHSNER, ALTON, and DEBAKEY, MICHAEL: Scleroderma; surgical considerations, *New Orleans Med. and Surg. Jr.*, 1939, xcii, 24-30.
569. O'DONOGHUE, D. H.: Internal derangements of the knee, *Jr. Oklahoma Med. Assoc.*, 1939, xxxii, 113-118.
570. OLIN, H. A.: The intervertebral disc: involvement in vertebral fractures and in spinal pathology, *Am. Jr. Roentgenol.*, 1939, xlii, 235-245.
571. OPPENHEIMER, ALBERT: Rickets of the spinal column, *Radiologia Clinica*, 1939, viii, 332-338.
572. ORGAIN, E. S., and POSTON, M. A.: Gonococcal endocarditis with recovery after sulfa-pyridine: report of a case, *New England Jr. Med.*, 1939, ccxxi, 167-169.
573. OSGOOD, E. E., BAKER, R. L., BROWNLEE, INEZ E., OSGOOD, MABLE W., ELLIS, DOROTHY M., and COHEN, WILLIAM: Total, differential and absolute leucocyte counts and sedi-

- mentation rates of healthy adolescents fifteen to eighteen years of age, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 905-912.
574. OSGOOD, E. E., BROWNEE, INEZ E., OSGOOD, MABLE W., ELLIS, DOROTHY M., and COHEN, WILLIAM: Total, differential and absolute leukocyte counts and sedimentation rates: determined for healthy persons nineteen years of age and over, *Arch. Int. Med.*, 1939, lxiv, 105-120.
575. OSGOOD, E. E., BAKER, R. L., BROWNEE, INEZ E., OSGOOD, MABLE W., ELLIS, DOROTHY M., and COHEN, WILLIAM: Total, differential and absolute leukocyte counts and sedimentation rates of healthy children four to seven years of age, *Am. Jr. Dis. Child.*, 1939, lviii, 61-70.
576. OSGOOD, E. E., BAKER, R. L., BROWNEE, INEZ E., OSGOOD, MABLE W., ELLIS, DOROTHY M., and COHEN, WILLIAM: Total, differential and absolute leukocyte counts and sedimentation rates for healthy children; standards for children eight to fourteen years of age, *Am. Jr. Dis. Child.*, 1939, lviii, 282-294.
577. OWEN, W. B.: A consideration of the problem of low back pain—the orthopedic point of view, *Kentucky Med. Jr.*, 1939, xxxvii, 182-183.
578. OWENS, C. A., WRIGHT, W. D., and LEWIS, M. D.: The value of fever therapy in sulfanilamide-resistant gonorrhea, *Jr. Urol.*, 1938, xl, 847-853.
579. OXFORD, T. M., and REED, C. R., JR.: Arthritis of the spine, *Tri-State Med. Jr.*, 1939, xii, 2363-2365.
580. PADULA, R. D., and KEYS, R. C.: Herniation of intervertebral discs, *Jr. Connecticut Med. Soc.*, 1939, iii, 552-559.
581. PAFF, G. H.: The action of colchicine upon the 48-hour chick embryo, *Am. Jr. Anat.*, 1939, lxiv, 331-349.
582. PAGEL, WALTER: Rheumatism, allergy, tuberculosis, *Papworth Research Bull.*, 1938, ii, 95-105.
583. PAPFORTH, SIDNEY: Retropulsion of the nucleus pulposus. A critical review, *Brit. Med. Jr.*, 1939, ii, 1038-1040.
584. PAPURT, L. E.: Osteoarthritis of the spine: its cost to industry, *Ohio State Med. Jr.*, 1939, xxxv, 743-746.
585. PARKER, GEOFFREY: Surgery in the treatment of rheumatic conditions, *Rheumatism*, 1939, i, 25-33 (April).
586. PARKER, R. L., and WILLIUS, F. A.: Cardiac clinics. LVII. Clinic on acute rheumatic pericarditis and myocarditis with acute cardiac dilatation, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 164-168.
587. PARSONS, E. H.: Physiological principles of fever therapy, *Med. Rec.*, 1939, cl, 96-100.
588. PARSONS, P. B., and POSTON, MARY A.: The pathology of human brucellosis: report of four cases with one autopsy, *South. Med. Jr.*, 1939, xxxii, 7-13.
589. PARSONS, R. P.: Gonorrhea today, *U. S. Nav. Med. Bull.*, 1939, xxxvii, 67-73.
590. PATTERSON, J. W. T.: The uses and limitations of hydrotherapy in the treatment of chronic rheumatism, *Clin. Jr.*, 1939, lxviii, 186-190.
591. PELOUZE, P. S.: Gonorrhea and sulfanilamide: an effort toward clinical orientation, *Am. Jr. Syph., Gonorr., and Ven. Dis.*, 1939, xxiii, 48-53.
592. PEMBERTON, RALPH: Considerations bearing on the treatment of arthritics, *Am. Jr. Med. Sci.*, 1939, cxcviii, 589-594.
593. PENNINGTON, DRURY: The contribution of the hydrotherapist to the rheumatic problem, *Brit. Jr. Rheumat.*, 1939, ii, 3-13.
594. PERKINS, GEORGE: Manipulation of difficult joints, *Brit. Med. Jr.*, 1938, ii, 1269-1270.
595. PERROTT, G. ST. J., TIMBITS, CLARK, and BRITTEN, R. H.: The national health survey. Scope and method of the nation-wide canvass of sickness in relation to its social and economic setting, *Pub. Health Rep.*, 1939, liv, 1663-1687.
596. PETHER, G. C.: The influence of industry on the development of rheumatism, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 433-440.

597. PHILLIPS, KENNETH: Fever therapy by physical means, *Arch. Phys. Therap.*, 1939, xx, 504-508.
598. PHILLIPS, R. T.: Plaster splints: a note on their value in the prevention and correction of arthritic deformities, *Rheumatism*, 1939, i, 30-31 (Oct.).
599. PILLMAN-WILLIAMS, E. C.: Diet as it affects rheumatism, *Med. Officer*, 1939, lxi, 208-210.
600. PLUMMER, NORMAN, and ENSWORTH, HERBERT: Sulfapyridine in the treatment of pneumonia, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1847-1854.
601. POATE, H. R. G.: Perforating injuries of joints, *Med. Jr. Australia*, 1939, i, 339-342.
602. POTTER, DOROTHY G. E.: Metabolism in arthritis and allied conditions, *Harrogate Spa Med. Jr.*, 1938, i, 10-20.
603. POTTS, F. N.: Tuberculosis of tendons, tendon sheaths and bursas, about the hand, *New York State Jr. Med.*, 1939, xxxix, 983-989.
604. POULTON, E. P.: Local tissue anoxia and its treatment with special reference to rheumatic myocarditis, *Lancet*, 1939, ii, 305-309.
605. POUNDERS, C. M., and GRAY, J. K.: Juvenile rheumatism, *South. Med. Jr.*, 1939, xxxii, 471-475.
606. PRESTON, R. L.: Treatment of acute staphylococcic suppurative arthritis, *Am. Jr. Surg.*, 1939, n.s. xlv, 195-200.
607. PRICE, N. L.: Gout following salyrgan diuresis, *Lancet*, 1939, i, 22-23.
608. PRINGLE, G. L. K.: Mass attack on chronic arthritis, *Edinburgh Med. Jr.*, 1939, xlv, 497-500.
609. RABSON, S. M.: Pathologic anatomy of human brucellosis, *Am. Jr. Clin. Path.*, 1939, ix, 604-614.
610. RACKEMANN, F. M., and GREENE, J. E.: Periarteritis nodosa and asthma, *Trans. Assoc. Am. Physicians*, 1939, liv, 112-118.
611. RADNOR, I.: Polyarticular arthritis treated with oestrogenic hormone, *Brit. Med. Jr.*, 1939, i, 505-506.
612. RAGSDALE, H. C.: Treatment of undulant fever with sodium cacodylate, *Jr. Indiana Med. Assoc.*, 1939, xxxii, 314.
613. RAMABHADHAN, K. G.: Liquor arsenicalis in the treatment of chorea, *Indian Med. Gaz.*, 1939, lxxiv, 161-162.
614. RAVENNA, PAOLO: A review of recent Italian work on rheumatism; I. Rheumatic fever, *Ann. Rheumat. Dis.*, 1939, i, 167-179.
615. RAWLS, W. B.: The relief of arthritic symptoms following urticaria, *Jr. Am. Med. Assoc.*, 1939, cxii, 2509-2510.
616. RAWLS, W. B.: The thyroid in chronic arthritis, *Rheumatism*, 1939, i, 11-18 (Oct.).
617. RAWLS, W. B., GRUSKIN, B. J., RESSA, A. A., and GORDON, A. S.: The relation between skin sensitivity, liver function, leucopenic index, and toxic effects from cinchophen, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 597-601.
618. RAWLS, W. B., WEISS, SAMUEL, and COLLINS, VERA L.: Liver function in rheumatoid (chronic infectious) arthritis, *ANN. INT. MED.*, 1939, xii, 1455-1462.
619. RAYCROFT, J. E.: Occupational therapy, *Hospitals*, 1938, xii, 92-94.
620. REDDICK, W. G.: The use of sulfanilamide in general medicine, *Tri-State Med. Jr.*, 1939, xi, 2299-2301, 2305-2306.
621. REEVES, J. R.: Use of skin tests in the diagnosis and treatment of rheumatoid arthritis, *Ohio State Med. Jr.*, 1939, xxxv, 1299-1301.
622. REICH, N. E.: A review of recent concepts of urinary lithiasis, with special reference to uric-acid stones; stone-forming danger during treatment for edema, with report of a case, *Internat. Clin.*, 1939, s. 2, iv, 232-281.
623. REIFENSTEIN, E. C., REIFENSTEIN, E. C., JR., and REIFENSTEIN, G. H.: A variable symptom complex of undetermined etiology with fatal termination, including conditions described as visceral erythema group (Osler), disseminated lupus erythematosus,

- atypical verrucous endocarditis (Libman-Sacks), fever of unknown origin (Christian) and diffuse peripheral vascular disease (Baehr and others), *Arch. Int. Med.*, 1939, lxiix, 553-574.
624. REIFENSTEIN, G. H.: A case of erythremia, gout and subleukemic myelosis, *Am. Jr. Med. Sci.*, 1939, cxcvii, 215-219.
625. REIMANN, H. A.: Infectious diseases, *Arch. Int. Med.*, 1939, lxiv, 362-405.
626. RHINELANDER, F. W., II, BENNETT, G. A., and BAUER, WALTER: Exchange of substances in aqueous solution between joints and the vascular system, *Jr. Clin. Invest.*, 1939, xviii, 1-13.
627. RHODES, A. J., and VAN ROOYEN, C. E.: An infective disease of uncertain etiology in a laboratory stock of rats, *Jr. Path. and Bact.*, 1939, xlix, 577-579.
628. RICHISON, EARL: Chronic arthritis, *U. S. Nav. Med. Bull.*, 1939, xxxvii, 61-66.
629. RITCHIE, W. T.: Acute rheumatic carditis (St. Cyres lecture), *Lancet*, 1939, ii, 581-585.
630. RITTER, ROBERT: Treatment of low back pain, *Surg. Clin. N. Am.*, 1939, xix, 35-41.
631. RIX, REGINALD: Dental infection and rheumatism, *Rheumatism*, 1938, i, 41-44 (July).
632. ROBERTS, W. R., and ROBERTS, E. L.: Undulant fever; a major public health problem, *Illinois Med. Jr.*, 1939, lxxv, 247-252.
633. ROBINSON, F. H., and EVANS, ALICE C.: Chronic brucellosis in Charlotte, North Carolina; report of cases, *Jr. Am. Med. Assoc.*, 1939, cxiii, 201-206.
634. ROGERS, M. H.: Treatment of subdeltoid bursitis, *Am. Jr. Surg.*, 1939, xliii, 292-297.
635. ROMER, FRANK: Treatment of chronic fibrositis by manipulation, *Post-Grad. Med. Jr.*, 1939, n.s. xv, 24-28.
636. ROPES, MARIAN W., BENNETT, G. A., and BAUER, WALTER: The origin and nature of normal synovial fluid, *Jr. Clin. Invest.*, 1939, xviii, 351-372.
637. ROPES, MARIAN W., ROSSMEISL, ELSIE, and BAUER, WALTER: The relationship between the erythrocyte sedimentation rate and the plasma proteins, *Jr. Clin. Invest.*, 1939, xviii, 791-798.
638. ROSENOW, E. C.: Experimental and clinical studies on the relation of streptococci to various diseases, *Illinois Med. Jr.*, 1939, lxxv, 28-38.
639. ROSENOW, E. C.: Recurring encephalomeningoradiculitis with fibromyositis following poliomyelitis; a bacteriologic study of sixty-four cases, *Arch. Int. Med.*, 1939, lxiv, 1197-1221.
640. ROSENTHAL, THEODORE, and WEINSTEIN, JOSEPH: Practical epidemiology of gonococcal infections in children, *New York State Jr. Med.*, 1939, xxxix, 718-722.
641. ROSSETT, N. E.: Skin reactions to an extract prepared from a gonococcus bouillon filtrate, *Yale Jr. Biol. and Med.*, 1939, xi, 345-354.
642. ROUND TABLE DISCUSSION ON RHEUMATIC FEVER: Eighth annual meeting of the American Academy of Pediatrics, *Jr. Pediat.*, 1939, xiv, 395-413.
643. ROUNTREE, J. T.: Herniation of the intervertebral disk—a report of two cases, *Virginia Med. Monthly*, 1939, lxvi, 103-105.
644. ROY, B. N. C.: Artificial fever therapy: electropyrexia, *Calcutta Med. Jr.*, 1939, xxxv, 449-455.
645. RUSSELL, A. R.: The complications of gonorrhea, *Jr. Oklahoma Med. Assoc.*, 1939, xxxii, 84-87.
646. SABIN, A. B.: Isolation of a filtrable, transmissible agent with "neurolytic" properties from toxoplasma-infected tissues, *Science*, 1938, lxxxviii, 189-191.
647. SABIN, A. B.: Identification of the filtrable, transmissible neurolytic agent isolated from toxoplasma-infected tissue as a new pleuropneumonia-like microbe, *Science*, 1938, lxxxviii, 575-576.
648. SABIN, A. B.: Experimental proliferative arthritis in mice produced by filtrable, pleuropneumonia-like microorganisms, *Science*, 1939, lxxxix, 228-229.

649. SABIN, A. B.: Mice as carriers of pathogenic pleuropneumonia-like microorganisms, *Science*, 1939, xc, 18-19.
650. SASHIN, DAVID, SPANBOCK, JOSEPH, and KLING, D. H.: Gold therapy in rheumatoid arthritis, *Jr. Bone and Joint Surg.*, 1939, xxi, 723-734.
651. SAUNDERS, J. B. DEC. M., and INMAN, V. T.: The intervertebral disc, a critical and collective review, *Internat. Abstr. Surg.*, 1939, lxi, 14-29.
652. SAVAGE, O. A., and TAYLOR, H. J.: Preliminary observations on the oxygen and carbon dioxide gas tensions in the knee-joint in normal and pathological conditions, *Ann. Rheumat. Dis.*, 1939, i, 134-140.
653. SAWYER, C. F.: Necrotizing arteritis (periarteritis nodosa), *Surgery*, 1939, vi, 717-721.
654. SCHLESINGER, BERNARD: Juvenile rheumatism, *Practitioner*, 1939, cxlii, 375-381.
655. SCHLESINGER, BERNARD: Chorea, *Brit. Jr. Rheumat.*, 1939, i, 229-236.
656. SCHMIDT, W. H.: Further development of physical therapy, *Arch. Phys. Therap.*, 1939, xx, 605-609.
657. SCHMIDT, W. H., and SMITH, J. L.: The sciatic syndrome and its management, *Arch. Phys. Therap.*, 1939, xx, 494-500.
658. SCHMITT, M. G.: Physiologic considerations of artificial fever therapy, *Arch. Phys. Therap.*, 1939, xx, 227-231.
659. SCHOENFELD, J.: Surgical derangements of the knee, *Jr. Am. Inst. Homeop.*, 1939, xxxii, 600-602.
660. SCHROEDER, M. C.: Recurrence of undulant fever following sulfonamide therapy, *Jr. Iowa Med. Soc.*, 1939, xxix, 453-455.
661. SCHULTZ, M. P.: The concentration of glutathione in the erythrocytes of patients with rheumatic fever, *Pub. Health Rep.*, 1939, liv, 264-268.
662. SCHULTZ, M. P.: Glucose tolerance in rheumatic fever, *Pub. Health Rep.*, 1939, liv, 305-310.
663. SCHULTZ, M. P.: Association between rheumatic fever and exophthalmic goiter, *Jr. Med.*, 1939, xx, 331-335.
Association between rheumatic fever and exophthalmic goiter, *Pub. Health Rep.*, 1939, liv, 373-380.
664. SCHULTZ, M. P.: Allergic irritability in rheumatic and nephritic patients, *Pub. Health Rep.*, 1939, liv, 1273-1279.
665. SCHULTZ, M. P., and ROSE, EDYTHE J.: The formol-gel reaction in rheumatic fever; an aid in the diagnosis of active carditis, *Pub. Health Rep.*, 1939, liv, 248-263.
666. SCHULTZ, M. P., and ROSE, EDYTHE J.: The catalytic potency of the blood in rheumatic fever, *Pub. Health Rep.*, 1939, liv, 343-352.
667. SCHUSTER, N. H.: Oxalate or citrate for the sedimentation test? *Lancet*, 1939, i, 872-874.
668. SCHWARTZ, B. A.: Rheumatic heart disease of the school child, *Jr. Med.*, 1939, xx, 425-427.
669. SCOTT, S. G.: X-ray therapy in rheumatic disease, *Rheumatism*, 1938, i, 1-16 (July).
670. SCOUGALL, STUART: Comparative anatomy of the knee joint in relation to congenital anomalies, *Med. Jr. Australia*, 1939, i, 691-694.
671. SCULL, C. W., BACH, T. F., and PEMBERTON, RALPH: Serum proteins in rheumatoid disease, *ANN. INT. MED.*, 1939, xii, 1463-1472.
672. SEDDON, H. J.: Inguinal lymph gland biopsy in the diagnosis of tuberculous disease of the knee, *Brit. Med. Jr.*, 1939, i, 105-107.
673. SELIG, SETH: Surgical treatment of chronic arthritis, *New York State Jr. Med.*, 1939, xxxix, 2114-2118.
674. SELL, STANLEY: Salicylate poisoning; report of a case, *Arch. Pediat.*, 1939, lvi, 55-57.
675. SEMMES, R. E.: Diagnosis of ruptured intervertebral disc without contrast myelography and comment upon recent experience with modified hemilaminectomy for their removal, *Yale Jr. Biol. and Med.*, 1939, xi, 433-435.

676. SHACKLE, J. W.: Laboratory investigations in chronic rheumatism, *Practitioner*, 1939, cxliii, 297-308.
677. SHAFAR, J.: Chorea and athetosis in childhood, *Brit. Jr. Child. Dis.*, 1938, xxxv, 259-266.
678. SHAFFER, M. F., and BENNETT, G. A.: The passage of type III rabbit virulent pneumococci from the vascular system into joints and certain other body cavities, *Jr. Exper. Med.*, 1939, lxx, 293-302.
679. SHANDS, A. R., JR.: The stabilization of joints in childhood, *Delaware State Med. Jr.*, 1939, xi, 231-235.
680. SHANNON, P. W.: Chronic back pain, *Jr. Med. Assoc. Alabama*, 1939, ix, 53-56.
681. SHAPIRO, M. J.: Differential diagnosis of nonrheumatic "growing pains" and subacute rheumatic fever, *Jr. Pediat.*, 1939, xiv, 315-322.
682. SHARPE, H. S.: Hyperparathyroidism associated with osteitis fibrosa cystica, *Canad. Med. Assoc. Jr.*, 1939, xl, 164-165.
683. SHAUGHNESSY, H. J., and GRUBB, T. C.: Reliability of the agglutination test for undulant fever, *Jr. Lab. and Clin. Med.*, 1938, xxiv, 298-307.
684. SHELTON, J. H., YOUNG, FREIDA, and DYKE, S. C.: Acute dermatomyositis; associated with reticulo-endotheliosis, *Lancet*, 1939, i, 82-84.
685. SHERWOOD, K. K., and HUTCHINS, L. R.: Charcot's joint, *Northwest Med.*, 1939, xxxviii, 257-260.
686. SHERWOOD, K. K., and THOMSON, MARIAN E.: Caloric and vitamin values in the diet of the arthritic patient, *Jr. Am. Dietet. Assoc.*, 1939, xv, 1-4.
687. SHORBE, H. B.: Chronic myositis of lumbar region; report on studies of fever therapy, *Arch. Phys. Therap.*, 1939, xx, 102-106.
688. SHRONT, J. F.: Undulant fever; its sources, modes of infection and prophylaxis, *Illinois Med. Jr.*, 1939, lxxvi, 373-380.
689. SHULLENBERGER, W. A.: Agranulocytosis following treatment of bacterial infections with sulfapyridine; case report with review of the literature, *Jr. Indiana Med. Assoc.*, 1939, xxxii, 415-417.
690. SIEBER, P. R.: Injuries of the knee joint, *Pennsylvania Med. Jr.*, 1939, xlii, 759-762.
691. SILBERBERG, MARTIN, and SILBERBERG, RUTH: Growth processes in cartilage and bone subsequent to gonadectomy and administration of anterior pituitary extract of cattle in immature male and female guinea pigs, *Am. Jr. Path.*, 1939, xv, 55-72.
692. SILBERBERG, MARTIN, and SILBERBERG, RUTH: A comparison of the effects of anterior pituitary hormone of skeletal tissues of young and mature guinea pigs, *Am. Jr. Path.*, 1939, xv, 547-560.
693. SILBERBERG, MARTIN, and SILBERBERG, RUTH: Action of estrogen on skeletal tissues of immature guinea-pigs, *Arch. Path.*, 1939, xxviii, 340-360.
694. SILBERBERG, MARTIN, and SILBERBERG, RUTH: Effect of potassium iodide on bone and cartilage in thyroidectomized immature guinea pigs, *Arch. Path.*, 1939, xxviii, 846-850.
695. SILVER, BARNEY, and ELLIOTT, MANNING: The use of sulfanilamide in 1,625 cases of gonorrhea in the male, *Jr. Am. Med. Assoc.*, 1939, cxii, 723-728.
696. SIMMONS, E. E., and DUNN, F. L.: Fever therapy in acute rheumatic disease, *Arch. Phys. Therap.*, 1939, xx, 547-553.
697. SKINNER, H. L., and ROUNTREE, J. T.: Herniation of the intervertebral disc and associated lesions—with report of cases, *Virginia Med. Monthly*, 1939, lxvi, 575-591.
698. SLOBODY, L. B., and MAFFIA, A. J.: Meningitis sympathica as an onset of Pott's disease, *Bull. New York Med. Coll., Flower and Fifth Ave. Hosps.*, 1939, ii, 116-119.
699. SLOT, G. M. J., and MORRIS, DAVID: Erythema nodosum associated with chorea and tuberculous meningitis, *Lancet*, 1939, i, 571-572.
700. SMART, MORTON: Physical medicine and industry, *Jr. Roy. Inst. Pub. Health and Hyg.*, 1939, ii, 419-432.

701. SMITH, A. D.: Diagnosis and treatment of sciatica, *Surg. Clin. N. Am.*, 1939, xix, 475-491.
702. SMITH, A. L.: Unnecessary treatment in mitral valve disease, *Nebraska State Med. Jr.*, 1939, xxiv, 49-55.
703. SMITH, C. H.: Dermatorrhesis (Ehlers-Danlos syndrome), *Jr. Pediat.*, 1939, xiv, 632-641.
704. SMITH, D. T., and POSTON, MARY A.: Some unusual cases of brucella infection, *Trans. Am. Clin. and Climat. Assoc.*, 1937, lii, 9-27.
705. SMITH, G. K.: Pott's disease in children, *Med. Jr. Australia*, 1939, ii, 303-308.
706. SMITH, K. M., and CURTIS, A. C.: Brucellosis with endocarditis; report of a case with failure of sulphanilamide therapy, *Am. Jr. Med. Sci.*, 1939, cxcviii, 342-346.
707. SMITH, P. W., KLEIN, A. D., and STECK, I. E.: The influence of vitamin D on the serum phosphatase activity in arthritis, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 1227-1237.
708. SMITH-PETERSEN, M. N.: Arthroplasty of the hip, a new method, *Jr. Bone and Joint Surg.*, 1939, xxi, 269-288.
709. SNOW, W. B.: The rationality, practicability and limitations of induced fever as a therapeutic agent, *Med. Rec.*, 1938, cxlviii, 448-452.
710. SNYDER, R. G.: The value of colonic irrigations in counteracting auto-intoxication of intestinal origin, *Med. Clin. N. Am.*, 1939, xxiii, 781-788.
711. SNYDER, R. G., TRAEGER, CORNELIUS, and KELLY, LEMOYNE: Gold therapy in arthritis; observations on 100 cases treated with gold sodium thiosulphate and aurocein, *ANN INT. MED.*, 1939, xii, 1672-1681.
712. SOMERS, D. C.: Generalized myositis fibrosa; report of a case, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 414-420.
713. SOSMAN, M. C.: Roentgenological aspects of acquired valvular heart disease, *Am. Jr. Roentgenol.*, 1939, xlii, 47-56.
714. SOUTHWORTH, HAMILTON, and COOKE, CRISPIN: Hematuria, abdominal pain and nitrogen retention associated with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 1820-1821.
715. SPAETH, A. V.: The treatment of lupus erythematosus with sulphanilamide, *Med. Rec.*, 1939, cl, 107-108.
716. SPAULDING, H. V.: The traumatic shoulder; with special reference to rupture of the supraspinatus tendon, *Am. Jr. Surg.*, 1939, xliii, 298-309.
717. SPINK, W. W.: The use of sulphanilamide in acute suppurative arthritis due to the hemolytic streptococcus, *Am. Jr. Med. Sci.*, 1939, cxcviii, 35-39.
718. SPINK, W. W.: The bactericidal effect of sulfanilamide upon pathogenic and non-pathogenic staphylococci, *Jr. Immunol.*, 1939, xxxvii, 345-358.
719. SPINK, W. W., and FLINK, E. B.: Sulfanilamide and sulfapyridine therapy, *Bull. Minnesota Med. Foundation*, 1939, i, 26-29.
720. SPURLING, R. G., and BRADFORD, F. K.: Low intraspinal lesions as a cause of back and sciatic pain, *Jr. Med.*, 1939, xix, 598-605.
721. SPURLING, R. G., and BRADFORD, F. K.: Low back and sciatic pain from the standpoint of the neurosurgeon, *Kentucky Med. Jr.*, 1939, xxxvii, 183-185.
722. SPURLING, R. G., and BRADFORD, F. K.: Neurologic aspects of herniated nucleus pulposus at the fourth and fifth lumbar interspaces, *Jr. Am. Med. Assoc.*, 1939, cxiii, 2019-2022.
723. STAMM, T. T.: Aetiology and treatment of osteo-arthritis, *Lancet*, 1939, ii, 754-756; 802-804.
724. STAMP, T. C.: Bacteriostatic action of sulphanilamide in vitro; influence of fractions isolated from haemolytic streptococci, *Lancet*, 1939, ii, 10-17.
725. STANLEY, CAMP: Observations on the use of chaulmoogra oil in arthritis, *Med. Ann. District of Columbia*, 1939, viii, 31-38.
726. STEEL, W. M.: Non-operative procedures for the relief of lumbo-sciatica, *Am. Jr. Surg.*, 1939, n.s. xlv, 76-87.

727. STEIN-LEWINSON, THEA: Handwriting in chronic arthritis; a paper in applied graphology, *Rheumatism*, 1938, i, 91-95 (Oct.).
728. STEINBERG, C. L., and SUTER, LOUISE C.: Phosphatase activity in chronic arthritis, *Arch. Int. Med.*, 1939, lxi, 483-492.
729. STEINBROCKER, OTTO: Local injections and regional analgesia with procaine solutions for intractable pain in chronic arthritis and related conditions, *ANN. INT. MED.*, 1939, xii, 1917-1939.
730. STEINDLER, A.: Differential diagnosis of low back pain, *Southwestern Med.*, 1939, xxiii, 7-9.
731. STEINDLER, A.: Mechanical derangement of knee, *Mississippi Valley Med. Jr.*, 1939, lxi, 158-163.
732. STEINER, W. R.: Gonorrheal meningitis; with report of a case and review of the literature, *Trans. Am. Climat. and Clin. Assoc.* (1936), 1937, lii, 1-8.
733. STERN, W. G.: Estimation of disability after injuries to bones and joints, *Jr. Am. Med. Assoc.*, 1939, cxii, 293-296.
734. STEVENS, HENRY: A short note on the relationship between oral sepsis and arthritis in prehistoric times, *Rheumatism*, 1939, i, 35-39 (July).
735. STEWART, A. B.: The identification of the haemolytic streptococci, with special reference to those of the upper respiratory tract, *Rheumat. Dis.*, 1939, i, 27-37.
736. STEWART, C. D., CLARK, D. E., DRAGSTEDT, L. R., and BECKER, S. W.: The experimental use of lipocain in the treatment of psoriasis, *Jr. Invest. Dermat.*, 1939, ii, 219-230.
737. STILES, M. H.: Sedimentation rate and nonfilament-filament ratio in low grade chronic illness; a statistical analysis of 292 cases, *Arch. Int. Med.*, 1939, lxi, 664-678.
738. SULLIVAN, E. R., and DIENES, L.: Pneumonia in white mice produced by a pleuropneumonia-like micro-organism, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 620-622.
739. SULLIVAN, M. X.: The significance of the cystine content of finger nails in arthritis, *Am. Jr. Surg.*, 1939, n.s. xliii, 620-625.
740. SUNDELL, C. E.: Some problems of the rheumatic child, *Post-Grad. Med. Jr.*, 1939, n.s. xv, 244-247.
741. SUTHERLAND, M. E.: Agranulocytosis following administration of M. & B. 693, *Lancet*, 1939, i, 1208-1209.
742. SWAIM, L. T.: The orthopaedic treatment of Strümpell-Marie arthritis, *Jr. Bone and Joint Surg.*, 1939, xxi, 983-991.
743. SWEETAPPLE, H. A.: The treatment of some late results of perforating injuries of joints, *Med. Jr. Australia*, 1939, i, 342-345.
744. SWEETAPPLE, H. A.: Septic arthritis of the knee joint, *Med. Jr. Australia*, 1939, i, 542-545.
745. SWETT, P. P.: The use of synovectomy in chronic arthritis, *New York State Jr. Med.*, 1939, xxxix, 2125-2131.
746. SWETT, P. P.: Varieties of healing process in tuberculosis of the spine, *Jr. Connecticut Med. Soc.*, 1939, iii, 652-655.
747. SWIFT, H. F., and BROWN, T. M.: Pathogenic pleuropneumonia-like microorganisms from acute rheumatic exudates and tissues, *Science*, 1939, lxxxix, 271-272.
748. SWIFT, H. F., and COHN, A. E.: Cardiac diseases, infectious and non-infectious, in relation to public health, *Trans. and Studies, Coll. Phys. Philadelphia*, 1938, s. 4, vi, 197-227.
749. SYMPOSIUM SECTION: Acute rheumatic fever, *Internat. Med. Digest.*, 1939, xxxv, 249-252.
750. SYNGE, V. M.: Rheumatic heart disease in practice, *Irish Jr. Med. Sci.*, 1939, 701-704.
751. TALBOTT, J. H., GALL, E. A., CONSOLAZIO, W. V., and COOMBS, F. S.: Dermatomyositis with scleroderma, calcinosis and renal endarteritis associated with focal cortical necrosis; report of a case in which the condition simulated Addison's disease, with comment on metabolic and pathologic studies, *Arch. Int. Med.*, 1939, lxi, 476-496.

752. TARR, LEONARD, and FERRIS, H. W.: Multiple myeloma associated with nodular deposits of amyloid in the muscles and joints and with Bence Jones proteinuria, *Arch. Int. Med.*, 1939, lxiv, 820-833.
753. TARSY, J. M.: Treatment of low back pain—by regional and local analgesic injections, *Indust. Med.*, 1939, viii, 186-193.
754. TAUSSIG, HELEN B.: Acute rheumatic fever; the significance and treatment of various manifestations, *Jr. Pediat.*, 1939, xiv, 581-592.
755. TAYLOR, R. S.: Oral infection and rheumatism, *Rheumatism*, 1938, i, 69-72 (Oct.).
756. TEGNER, WILLIAM: The present trend of gold therapy for arthritis in Europe, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 117-122.
757. TEGNER, W. S.: The treatment of the rheumatic diseases in the United States and the continent of Europe, *Ann. Rheumat. Dis.*, 1939, i, 249-303.
758. TERHUNE, S. R.: Chronic arthritis, *Jr. Med. Assoc. Alabama*, 1939, viii, 394-397.
759. TERHUNE, S. R.: Backache: a discussion of traumatic destruction of the lumbosacral intervertebral disc, *Mississippi Doctor*, 1939, xvii, 248-252.
760. THAMES, E.: Exploring the possibilities of afebrile brucellosis, *Jr. Med. Assoc. Alabama*, 1939, viii, 245-253.
761. THOMAS, CAROLINE B., and FRANCE, RICHARD: A preliminary report of prophylactic use of sulfanilamide in patients susceptible to rheumatic fever, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 67-77.
762. THOMPSON, A. R.: Some aspects of cancer of the prostate, *Guy's Hosp. Rep.*, 1938, lxxxviii, 418-421.
763. THOMPSON, B. C.: Erythema nodosum associated with acute tuberculous cervical lymphadenitis, *Brit. Med. Jr.*, 1939, i, 159-162.
764. THOMPSON, EDWARD: Rheumatic fever in Nebraska, *Nebraska State Med. Jr.*, 1939, xxiv, 347-349.
765. THOMSON, L. C.: Polyarticular osteoarthritis in a young man, associated with chondro-osseous dystrophy, *Guy's Hosp. Rep.*, 1938, lxxxviii, 446-455.
766. TIMMES, J. J.: Hypertrophied ligamentum flavum, *U. S. Nav. Med. Bull.*, 1939, xxxvii, 538-541.
767. TISLOWITZ, RICHARD: The action of estrogens in inducing mitoses in the muscle, connective tissue and epithelium of the prostate and seminal vesicle of mice as determined by the colchicine technique, *Anat. Rec.*, 1939, lxxv (suppl.), 265-273.
768. TISLOWITZ, R.: The colchicine test as a method for determining the time of onset and the duration of action of male active substances, *Endocrinology*, 1939, xxv, 749-753.
769. TITUS, N. E.: The value of electrical treatment of subdeltoid bursitis, *Med. Rec.*, 1939, cl, 354-357.
770. TOBIAS, NORMAN: The modern management of psoriasis, *Internat. Clin.*, 1939, s. 2, iii, 173-182.
771. TOLSTOL, EDWARD: Preventive aspects of disorders of metabolism: gout, obesity, and diabetes mellitus, *Prevent. Med.*, 1939, ix, 6-20.
772. TOUMEY, J. W., JR.: Knee joint tuberculosis: two hundred twenty-two patients treated by operative fusion, *Surg., Gynec. and Obst.*, 1939, lxviii, 1029-1037.
773. TRAUT, E. F.: Dissociation of streptococci in arthritis, *Acta rheumatol.*, 1938, x, 4-5.
774. TRAUT, E. F., and LOGAN, C. E.: Preliminary report on the use of sulfanilamide, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 604-608.
775. TRAUT, E. F., and VRTIAK, E. G.: A statistical study of allergy in arthritis, *ANN. INT. MED.*, 1939, xiii, 761-767.
776. TROUP, W. A.: Physio-therapy: I. Infra-red irradiation in the treatment of rheumatism, *Rheumatism*, 1939, i, 42-47 (July).
777. TUCK, V. L.: Injuries of the knee joint, *Texas State Jr. Med.*, 1939, xxxiv, 607-610.
778. URBACH, ERICH, and THOMAS, C. C.: Classification and definition of the clinical varieties of erythematodes (lupus erythematosus), with particular reference to its acute and subacute course, *Brit. Jr. Dermat. and Syph.*, 1939, li, 343-358.

779. VAIZEY, J. M., and CLARK-KENNEDY, A. E.: Dental sepsis in relation to anaemia, dyspepsia, and rheumatism with particular reference to treatment, *Brit. Med. Jr.*, 1939, i, 1269-1273.
780. VALLS, JOSE: Ruptures of the lateral ligaments of the knee joint, *Am. Jr. Surg.*, 1939, xliii, 486-491.
781. VANCE, E. B. M.: The stiff joint, *Med. Jr. Australia*, 1939, i, 139-145.
782. VAN DYKE, H. B., GREEP, R. O., RAKE, GEOFFREY, and McKEE, C. M.: Observations on the toxicology of sulfathiazole and sulfapyridine, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 410-416.
783. VASSILIADIS, H. C.: Fever treatment of gonorrhea, *Chinese Med. Jr.*, 1938, liv, 454-463.
784. VOIGHT, W. W.: The menopause and painful stiffening of shoulder, *Illinois Med. Jr.*, 1939, lxxv, 340-344.
785. VORHAUS, M. G., and KRAMER, M. L.: Studies on thiamin chloride in gout, *Acta rheumatol.*, 1938, x, 8-11.
786. VOSS, J. A.: Some experiences with the vaccine treatment of chronic rheumatic diseases, *Rheumatism*, 1938, i, 67-68 (Oct.).
787. VRTIAK, E. G., and KOBAC, D.: Further studies with fango therapy, *Arch. Phys. Therap.*, 1939, xx, 487-493.
788. WADDILL, J. F.: Clinical manifestations of acute rheumatic fever: age incidence, diagnosis and treatment, *Virginia Med. Monthly*, 1939, lxvi, 322-329.
789. WADE, J. L.: Gout: an ancient wolf in modern sheep's clothing, *West Virginia Med. Jr.*, 1939, xxxiii, 128-136.
790. WAGONER, GEORGE: Chronic sciatic pain due to adhesions about the nerve trunk and the results of their removal by operation, *Surgery*, 1939, v, 609-613.
791. WALKER, J. A. L.: Low back pain and sciatica, *Canad. Med. Assoc. Jr.*, 1939, xl, 240-247.
792. WALLGREN, ARVID: Renal lesions in children with erythema nodosum, *Arch. Dis. Childhood*, 1939, xiv, 271-274.
793. WALSH, M. N., and LOVE, J. G.: The syndrome of the protruded intervertebral disk, *Proc. Staff Meet. Mayo Clin.*, 1939, xiv, 230-234.
794. WALTON, L. H. F.: Notes on a case of bilateral arthritis of the hip-joints treated by capsulectomy, *Proc. Roy. Soc. Med.*, 1939, xxxii, 827-830.
795. WALTON, S. T.: A quick and reliable method for staining gonococcus smears, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 1308-1309.
796. WARNER, O. M.: Osteitis tuberculosa multiplex cystica of the knee and elbow, *Med. Bull. Vet. Adminis.*, 1939, xv, 304-306.
797. WAUGH, J. R.: Peripheral neuritis during administration of sulfanilamide, *Am. Jr. Syph., Gonorr., and Ven. Dis.*, 1939, xxiii, 745-750.
798. WAUGH, J. R., and DAWBER, T. R.: Four hundred and seventy-three hospitalized male gonorrhea patients treated with sulfanilamide, *Am. Jr. Syph., Gonorr., and Ven. Dis.*, 1939, xxiii, 477-489.
799. WAUGH, W. G.: The problem of arthritic deformity, *Newcastle Med. Jr.*, 1938, xviii, 131-142.
800. WAUGH, W. G.: The treatment of arthritic deformity by lactic acid injection, *Rheumatism*, 1939, i, 15-23 (July).
801. WEBER, M. L.: A clinical and roentgenological analysis of 150 cases of chronic non-specific arthritis, *Med. Bull. Vet. Admin.*, 1939, xv, 243-260.
802. WEINBERGER, L. M.: Non-traumatic paralysis of dorsal interosseous nerve, *Surg., Gynec. and Obst.*, 1939, lxix, 358-363.
803. WEINER, HARRY: Vaccine therapy in the rheumatic patient, *New York State Jr. Med.*, 1939, xxxix, 1786-1789.
804. WEINSTEIN, ALBERT: The problem of arthritis, *Jr. Tennessee Med. Assoc.*, 1939, xxxii, 113-119.

805. WEIR, D. R.: Polyarteritis nodosa. Report of a case, *Am. Jr. Path.*, 1939, xv, 79-88.
806. WEISSTUB, I.: Back to the old treatment of gonorrhoea, *Canad. Med. Assoc. Jr.*, 1939, xl, 389.
807. WENDEL, W. B.: The control of methemoglobinemia with methylene blue, *Jr. Clin. Invest.*, 1939, xviii, 179-185.
808. WESSON, A. S.: Discussion on manipulation in rheumatic disorders, *Proc. Roy. Soc. Med.*, 1939, xxxii, 275-278.
809. WEST, E. F.: Some aspects of operations for internal derangements of the knee joint, *Med. Jr. Australia*, 1939, i, 380-382.
810. WHEELDON, THOMAS: What message should the specialist carry to the family physician in regard to the treatment of arthritis, *Virginia Med. Monthly*, 1939, lxvi, 670-674.
811. WHEELDON, T. F., and BOSHER, L. H., JR.: A biochemical investigation of arthritis; preliminary report on uric acid, glutathione, and sulfur in the blood; and sulfur in the urine, *Am. Jr. Surg.*, 1939, n.s. xliii, 598-619.
812. WHITE, P. A.: Acute rheumatic fever, *Hygeia*, 1939, xvii, 43-44.
813. WIECHEC, F. J., and KRUSEN, F. H.: A new method of joint measurement and a review of the literature, *Am. Jr. Surg.*, 1939, n.s. xliii, 659-668.
814. WILLIAMS, H. L., and SLOCUMB, C. H.: Nasal accessory sinuses as foci of infection in arthritis, *Arch. Otolaryng.*, 1939, xxix, 829-834.
815. WILSON, I. D.: Bang's disease, *Virginia Med. Monthly*, 1939, lxvi, 142-143.
816. WILSON, J. F.: Sulfanilamide in the treatment of acute lupus erythematosus; failure with well controlled administration, *Arch. Dermat. and Syph.*, 1939, xl, 241-243.
817. WILSON, S. J., and DOAN, C. A.: Pathogenesis of hemorrhage in artificially induced fever, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 115-117.
818. WINER, L. H., and LEIBOVITZ, A.: Gonococcus cultures as an aid to diagnosis, *Journal-Lancet*, 1939, lix, 267.
819. WINTERS, MATTHEW, PETERS, G. A., and CROOK, GRACE W.: Pectin as a prophylactic and curative agent for peptic ulcers produced experimentally with cinchophen, *Am. Jr. Digest. Dis.*, 1939, vi, 12-15.
820. WISHENGRAD, MICHAEL: Gonococcus filtrate test for gonorrhea, *Urol. and Cutan. Rev.*, 1939, xliii, 386-389.
821. WOLFE, S. G.: Undulant fever, *Tri-State Med. Jr.*, 1939, xi, 2220-2221.
822. WOODWARD, KING: Signs and symptoms of rheumatic fever, *Illinois Med. Jr.*, 1939, lxxvi, 526-527.
823. WOOTTON, W. T.: An analysis and discussion of positive food reactions in 500 individuals afflicted with arthritis or rheumatoid conditions, *Jr. Arkansas Med. Soc.*, 1939, xxxvi, 67-69.
824. WRIGHT, L. T., and LOGAN, MYRA: Osseous changes associated with lymphogranuloma venereum, *Arch. Surg.*, 1939, xxxix, 108-121.
825. WRIGHT, SAMSON: Physiological aspects of rheumatism, *Proc. Roy. Soc. Med.*, 1939, xxxii, 651-662.
826. WYATT, B. L., THOMPSON, H. E., and FRANCIS, J. D.: Chronic arthritis; differential diagnosis and special treatment methods: medical, orthopedic, physical therapy, *New York State Jr. Med.*, 1939, xxxix, 2037-2042.
827. YANDELL, H. R.: Experience with the use of prontosil. Case report, *Jr. Oklahoma Med. Assoc.*, 1939, xxxii, 51-52.
828. YEOMAN, W.: Observations on the sedimentation rate in cases of rheumatoid arthritis under treatment, *Harrogate Spa Med. Jr.*, 1938, i, 5-10.
829. YOUNG, JAMES: Pelvic osteo-arthritis of pregnancy, *Proc. Roy. Soc. Med.*, 1939, xxxii, 1591-1597.
830. YOUNG, R. H.: The stiff shoulder, *St. Thomas's Hosp. Gaz.*, 1939, xxxvii, 65-69.
831. ZADEK, ISADORE: An operation for the cure of achillobursitis, *Am. Jr. Surg.*, 1939, n.s. xliii, 542-546.

Books, 1938-1939

These books appeared during 1938-1939 but were *not* reviewed herein

1. AMERICAN MEDICAL ASSOCIATION COUNCIL ON PHYSICAL THERAPY: Handbook of physical therapy; selections authorized for publication by the Council on Physical Therapy, American Medical Association, Ed. 3, 1939, American Medical Association, Chicago, Illinois, 436 pp.
2. BURROWS, H. J., and COLTART, W. D.: Treatment by manipulation [n. d.], Published by "The Practitioner," Eyre & Spottiswoode, Ltd., London, 36 pp.
3. COPEMAN, W. S. C.: The treatment of rheumatism in general practice, Ed. 3, 1939, William Wood & Co., Baltimore, 276 pp.
4. CROWE, H. W.: Rheumatism, 1939, John Bale Medical Pub'ns, Ltd., London, 280 pp.
5. FERGUSON, A. B.: Roentgen diagnosis of the extremities and spine, Annals of Roentgenology, vol. xvii, 1939, Paul B. Hoeber, Inc., New York, 435 pp.
6. FISHER, A. G. T.: Treatment by manipulation in general and consulting practice, Third edition of "Manipulative Surgery," 1939, H. K. Lewis & Co., Ltd., London, 267 pp.
7. FOX, HERBERT: Chronic arthritis in wild mammals. Transactions of the American Philosophical Society held at Philadelphia for promoting useful knowledge, 1939, n.s. vol. xxxi, pt. ii, Philadelphia, pp. 73-148.
8. GHORMLEY, R. K., editor: Orthopedic surgery (chapter on acute and chronic arthritis, etc.), 1938, Thomas Nelson & Sons, New York, 727 pp.
9. HODGES, P. C., AND OTHERS: The roentgen-ray diagnosis of diseases of the bones and joints, 1938, Thomas Nelson & Sons, New York, 250 pp.
10. MENNELL, JAMES: The science and art of joint manipulation, vol. i: The extremities, 1939, J. & A. Churchill, Ltd., London, 233 pp.
11. MONROE, R. T.: Chronic arthritis. [Reprinted from Oxford Loose-Leaf Medicine], 1939, Oxford University Press, New York, 84 pp.
12. NISSÉ, B. S.: Rheumatism, 1938, John Bale Medical Pub'ns, Ltd., London, 168 pp.
13. SCHNEIDER, E. C.: Physiology of muscular activity, Ed. 2, 1939, W. B. Saunders Company, Philadelphia, 428 pp.

CASE REPORTS

THE SIGNIFICANCE OF SPLITTING OF THE P-WAVE IN THE ELECTROCARDIOGRAM *

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NOTCHING, bifurcation and splitting of the P-wave have been observed in a variety of cardiac conditions. The feature which is common to all and which is responsible for the abnormality can best be understood by considering a few facts relative to the time of onset of the contraction of the two auricles and the modifications that follow experimental interference with the spread of the wave of excitation from one auricle to the other.

An old observation of Chauveau¹ made on the horse in 1894, that the right auricle contracts before the left, was confirmed experimentally by Fredericq^{2,3} using the dog's heart, and subsequently by his pupils Schmidt-Nielsen⁴ and Stassen,⁵ who found a time interval of 0.03–0.04 sec. Garten⁶ and Erfmann⁷ obtained by local derivation of the action current, an interval of 0.013–0.014 sec. Lewis, Meakins and White⁸ concluded from their measurements that the question as to whether right or left auricle first contracts is unprofitable since "certain portions of the right auricle contract before certain portions of the left auricle, and vice versa." But, as was pointed out by the writer,⁹ although it is doubtless true that individual parts of the two auricles begin their contraction at various times in reference to each other, it is the resultant of these differently timed contractions that determines the contraction of the chamber as a whole. A priori reasoning would lead one to expect that the right auricle being nearer the site of impulse formation would be the first to receive the excitation and would therefore contract before the left. Using the suspension method in 12 dogs, the author was able to confirm the observation that the right auricle contracts before the left. An average of 332 measurements yielded a time interval of 0.013 sec. The author was also able to demonstrate that the most direct path of conduction from the sino-auricular node to the left auricle is the interauricular bundle—a bundle of muscle fibers that stretches from the head of the S–A node to the base of the left auricular appendage. Clamping this bundle causes a marked delay in the conduction of the impulse to the left auricle so that the interauricular time interval is prolonged from two to four times the normal average.⁹ The same results were obtained when Wiggers' miniature myographs and segment capsules were used. (See figures 1 and 2.) That in spite of the crushing of this band of muscle the impulse reaches the left auricle indicates that other less direct pathways exist.†

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† The various muscle bundles connecting the two auricles have been described by Papez.¹⁰ Besides the interauricular bundle, they include chiefly the left anterior crest and the septo-pulmonary bundles. Both sets of fibers intermingle more or less with those of the interauricular bundle.

This observation has since been confirmed by a number of investigators. In this connection the work of Rothberger and Scherf¹¹ is of special significance as their experiments included a study of the electrocardiogram. So far as this feature of their work is concerned, they found that ligation of the interauricular bundle was followed by splitting of the P-wave, which was often flattened out and at times became negative. Certain variations in their results led these investigators to ligate various branches of the coronary arteries that supplied the region of the heart under consideration. The effects observed were uncertain,

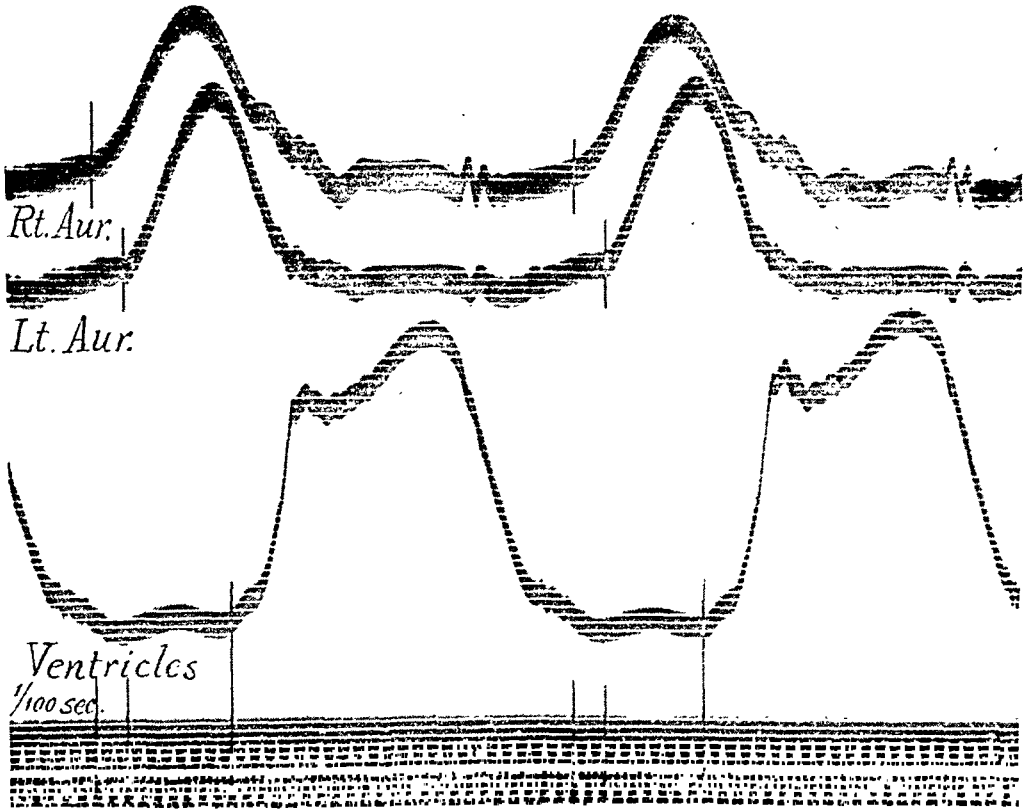


FIG. 1. Record of contraction of auricles and ventricles of the dog's heart. The left auricle contracts 0.02 sec. after the right auricle.

but clamping or ligation of the bundle in places where no blood vessels were visible led to the usual changes. This question was taken up subsequently by Condorelli¹² who described a branch of the left coronary artery under the name of *ramus recurrens interauricularis*, ligation of which caused the same effects as injury to the interauricular band. In the course of his experiments, there occurred on occasion a fibrillation of the left auricle while the right auricle continued beating rhythmically.

There can be little doubt, therefore, that direct injury to the interauricular bundle or serious interference with its blood supply will delay interauricular conduction and that this will manifest itself in the electrocardiogram as a splitting of the P-wave. The slight notching near the summit of P seen at times in the

normal electrocardiogram is probably due to an incomplete fusion of the potentials developed in the two auricles. Whether in such cases the interauricular time interval is greater than the average remains to be investigated.

A number of clinicians have in recent years directed their attention to the mechanism of bifurcation or complete splitting of the P-wave as seen in the human electrocardiogram. Among them may be mentioned Groedel,¹³ who reported three cases which, after consideration of various other possibilities, he believed might best be explained as due to an exaggerated asynchronism of the two auricles owing to interference with the conduction of the excitatory process. He seemed to be unaware, however, of the pathway that might be affected. Ac-

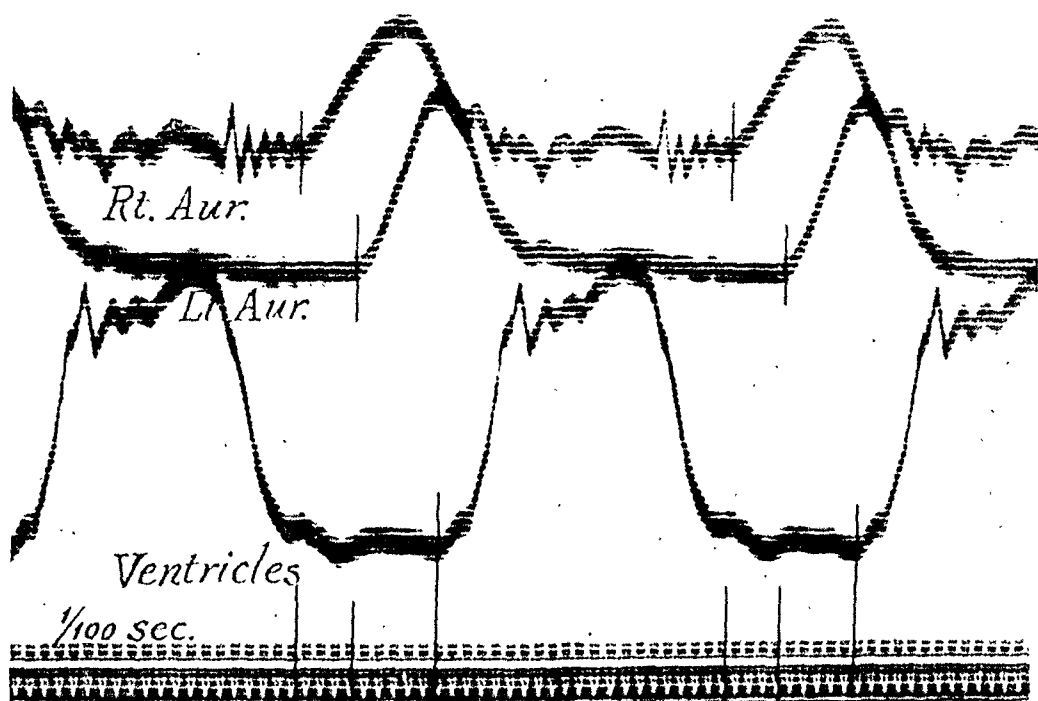


FIG. 2. Record of contraction of auricles and ventricles of the same heart as in figure 1 after clamping the interauricular bundle. The left auricle now contracts 0.04 sec. after the right auricle.

cording to Trendelenburg,¹⁴ it is possible by cross derivation to obtain evidence of the separate and asynchronous activation of the two auricles in the normal heart. By the use of chest leads suitably placed, von Boros,¹⁵ Laufer,¹⁶ Laufer and Rubino¹⁷ were able to demonstrate a prolongation of the interauricular time interval in cases in which a splitting of the P-wave occurred.

While these observations are in conformity with the experimental results presented above and point to the probability that the interference of conduction lies along the path of the interauricular bundle no one has, so far as the author is aware, studied this part of the heart in a case in which a notching or splitting of the P-wave had been observed. For this reason, the following report of histological findings in such a case is presented in the hope that further studies may be stimulated:

CASE REPORT

The patient was a white male, 53 years old, in whom a diagnosis of hypertension had been made two years previous to admission. About a year after this diagnosis was made, he had for the first time an attack of angina pectoris. Attacks recurred at intervals of a few months. Toward the end of the year he developed signs of congestive heart failure and at the time of admission was suffering from orthopnea. A diagnosis of arteriosclerotic heart disease and congestive heart failure was made.

An electrocardiogram taken on the day following admission was interpreted as indicative of coronary sclerosis and myocardial fibrosis. There occurred occasional nodal premature beats. Aside from the changes in the ventricular complexes, including a deep Q, the P-wave was deeply notched, especially in Leads I and II (figure 3).

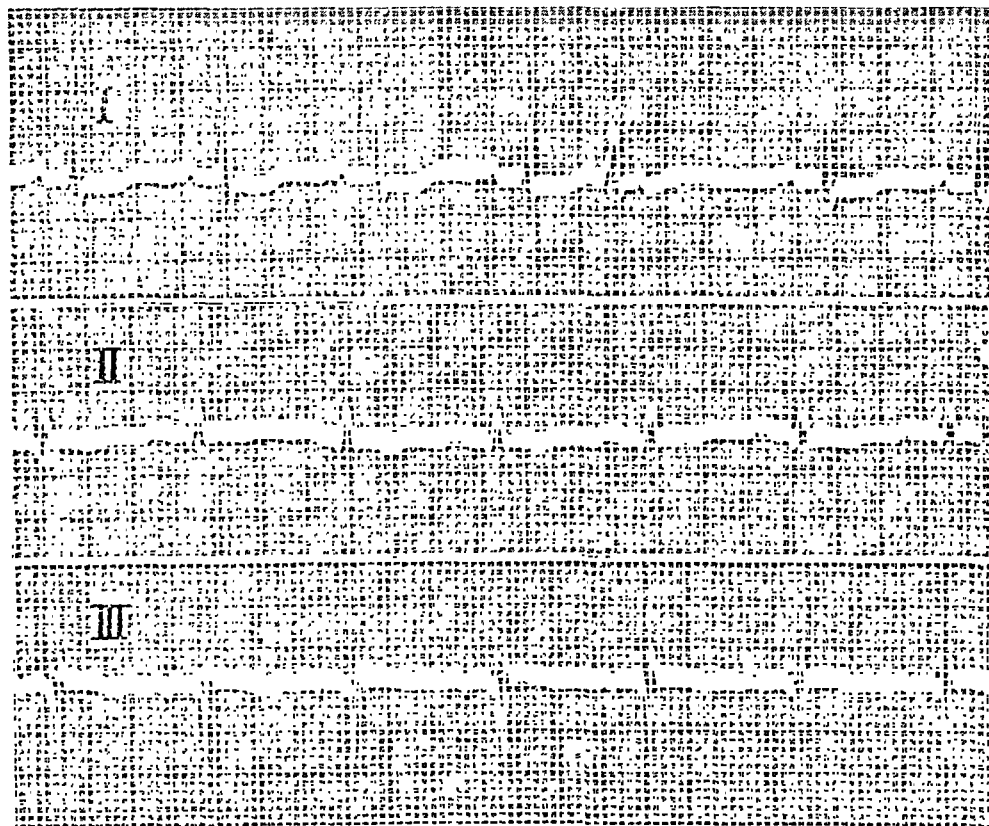


FIG. 3. Electrocardiogram obtained from the patient showing bifurcation of the P-wave in Leads I and II.

Autopsy: The patient died eight days after admission. At autopsy there were found a marked coronary sclerosis and massive cardiac hypertrophy, the heart weighing 870 grams. There were also found a well developed aortic atherosclerosis and an early arteriosclerotic nephritis. On inspection of the interauricular bundle, it was observed that a mass of fat overlaid it at about the position of the interauricular septum. The interauricular bundle had, of course, participated in the general hypertrophy.

After fixation of the whole heart in 10 per cent formalin, a block of tissue including the whole of the interauricular bundle was removed and prepared for histological study. A similar block of tissue was taken from a normal heart for com-

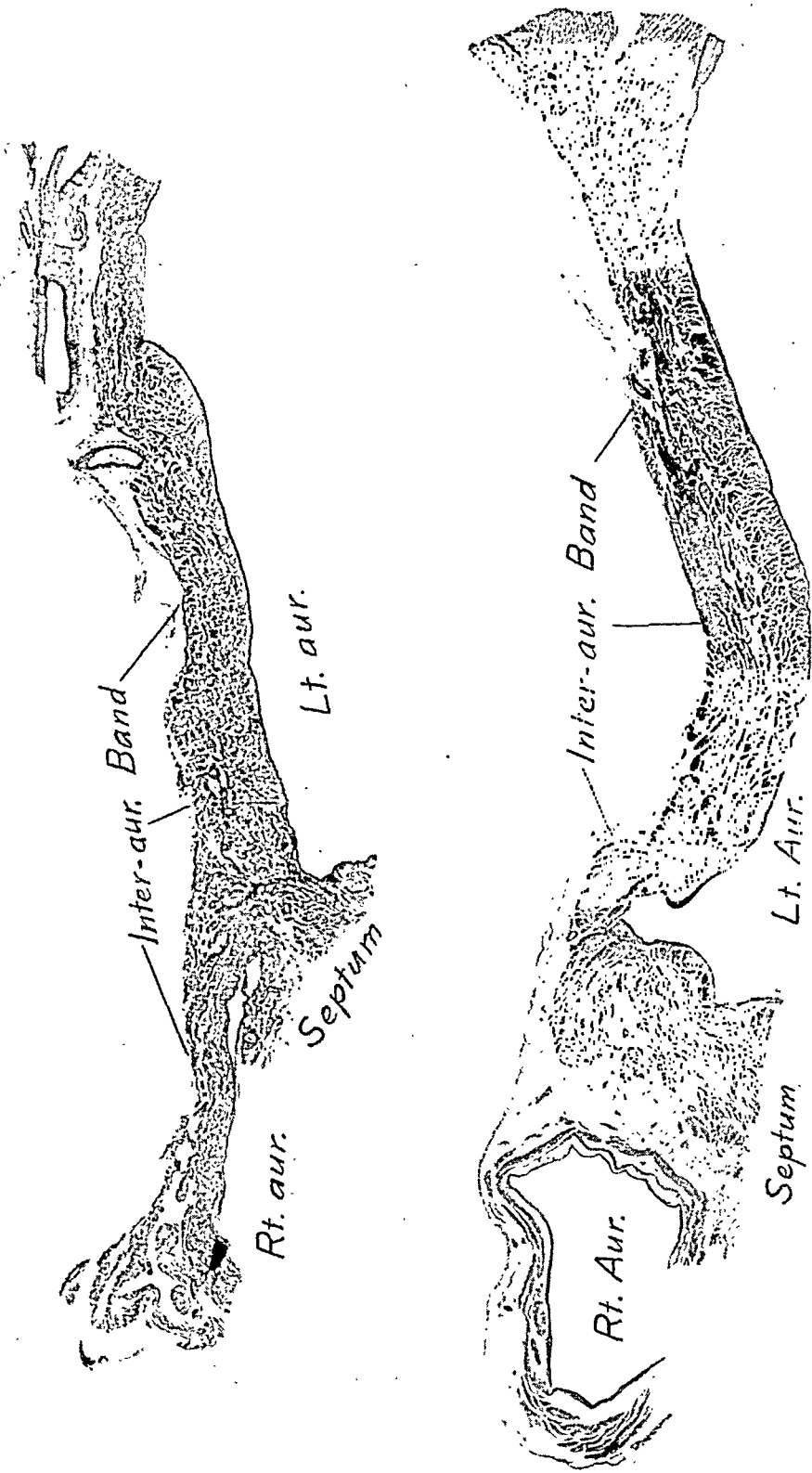


FIG. 4. Sections of the entire interauricular bundle at low magnification. Upper section from a normal heart. Lower section from the patient's heart.

parison. As these blocks were too long for section mounting, they were divided in two, immediately to the left of the interauricular septum before infiltration with paraffin. The sections were cut longitudinally 10 micra thick; every tenth section was mounted and stained with hematoxylin and eosin.



FIG. 5. Section of the interauricular bundle at the level of the septum showing fatty infiltration and separation of muscle masses. Magnification $\times 50$.

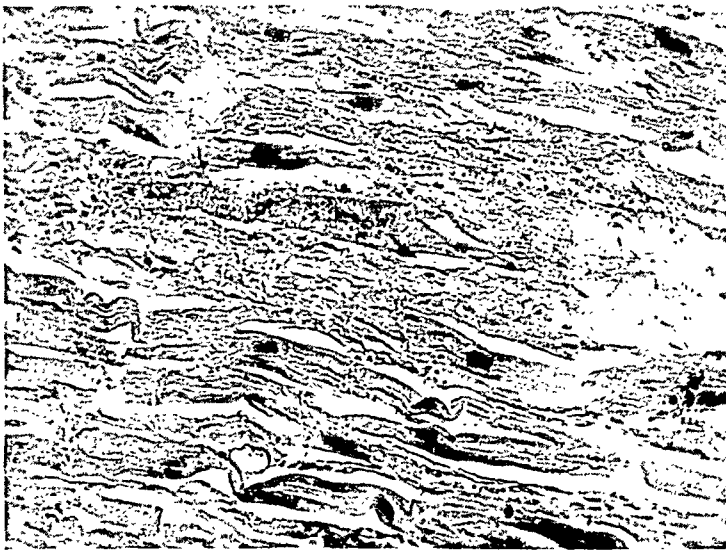


FIG. 6. Section of the interauricular bundle to the left of the septum showing swelling, fragmentation and degeneration of muscle fibers. Note the degenerated muscle fiber surrounded by connective tissue. Magnification $\times 150$.

Histopathology: Figure 4 shows the appearance at low magnification of a section of the entire bundle in the normal and diseased heart taken at about the middle third of its thickness. Since the magnification was the same, the relative size of the two specimens is apparent. The increase in interstitial connective tissue in the pathological specimen and the scarcity of muscle tissue across the septum are all evident.

Even at this low magnification an area of the muscle below and to the right of the central line leading from the lettering "Inter-aur. Band" can be seen to differ in appearance from the rest.

Photomicrographs were made of the upper part of the septum and of the area of muscle just mentioned. The first of these (figure 5) shows how fat tissue has infiltrated into the septum and has separated the muscle fibers on their way from the head of the S-A node to the left auricle. The second photomicrograph (figure 6) shows swelling, fragmentation and degeneration of the muscle fibers. The center of the section shows a degenerated muscle cell fading into fibrous tissue. These changes were found in various degree throughout the band.

DISCUSSION

It is evident that sufficient pathological alterations had taken place to interfere with the free conduction of the excitatory wave from the right to the left auricle and that, in accordance with the results of experiment, these alterations can account for the splitting of the P-wave observed in the electrocardiogram. This change in the form of the P-wave may therefore be expected in any condition in which interference with conduction through the interauricular bundle is likely to occur.

Aside from cardiac myopathies and disturbances of blood supply a splitting of the P-wave is often seen in mitral stenosis. It has been the custom to assign this change of form to hypertrophy of the left auricle and consequent prolongation in the spread of excitation through this chamber. The accuracy of this interpretation is doubtful. It is well known that in mitral stenosis the left auricle may become greatly distended. Rothberger¹⁸ has called attention to the circumstance that, as a consequence of the distention, a pressure atrophy of the musculature may occur. A wide separation of muscle fibers and connective tissue replacement follow which, because of its position, must implicate the interauricular bundle. Aneurysm of the left auricle will produce the same results. In a case of this condition reported by Mahaim,¹⁹ two P-waves separated by an interval of 0.1 sec. were recorded. Where the interauricular time interval is so greatly prolonged or where manifold splitting is seen, as in a case of mitral stenosis reported by Rothberger,¹⁸ the damage to the interauricular musculature may include other bundles in addition to the interauricular band. In any event, the interauricular bundle is the most important part of the interauricular musculature for conduction, as it not only conducts the excitatory process at a higher rate,⁸ but is also the most direct path from the S-A node to the left auricle.

SUMMARY

Notching, bifurcation and splitting of the P-wave of the electrocardiogram are due to prolongation of interauricular conduction time, the result of damage to the interauricular bundle. A case is reported in which the electrocardiogram showed deep notching of the P-wave and in which there were found post mortem marked pathological alterations of the interauricular bundle. Experiment had shown previously that this bundle is the chief pathway for the conduction of the excitatory process from the S-A node to the left auricle.

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BIBLIOGRAPHY

1. CHAUVEAU, A., quoted by ARLOING, S.: Modifications rares ou peu connues de la contraction des cavités du coeur sous l'influence de la section et des excitations des nerfs pneumogastriques, *Arch. d. physiol. norm. et pathol.*, 1894, vi, 5 s., 163-171.
2. FREDERICQ, L.: Sur les pulsations de la veine cave supérieure et des oreillettes du coeur chez le chien, *Bull. acad. roy. d. Belg.*, 1901, 130-131.
3. FREDERICQ, L.: La pulsation du coeur du chien est une onde de contraction qui débute dans l'oreillette droite, s'étend rapidement aux parois des deux oreillettes, puis franchit lentement le faisceau de His, pour s'irradier rapidement dans la substance des ventricules, *Arch. internat. d. physiol.*, 1906, iv, 37-75.
4. SCHMIDT-NIELSEN: Du prétendu synchronisme de la systole des deux oreillettes, *Arch. internat. d. physiol.*, 1907, iv, 417-433.
5. STASSEN: De l'ordre de succession des différentes phases de la pulsation cardiaque chez le chien, *Arch. internat. d. physiol.*, 1907, v, 60-75.
6. GARTEN, S.: Ueber die Verwendung der Differentialelektroden am Säugetierherzen, *Skand. Arch. f. Physiol.*, 1913, xxix, 114.
7. ERFMANN: Ein Beitrag zur Kenntnis der Fortleitung des Erregungsvorganges am Warmblüterherzen, *Ztschr. f. Biol.*, 1913, lxi, 155.
8. LEWIS, T., MEAKINS, J., and WHITE, P. D.: The excitatory process in the dog's heart. Part I. The auricles, *Phil. trans. roy. soc. London.*, s.B., 1914, ccv, 375-420.
9. BACHMANN, G.: The inter-auricular time interval, *Am. Jr. Physiol.*, 1916, xli, 309-320.
10. PAPEZ, J. W.: Heart musculature of the atria, *Am. Jr. Anat.*, 1920, xxvii, 255-277.
11. ROTHBERGER, C. J., and SCHERF, D.: Zur Kenntnis der Erregungsausbreitung vom Sinusknoten auf den Vorhof, *Ztschr. f. d. ges. exper. Med.*, 1927, liii, 792-835.
12. CONDORELLI, L.: Experimentelle Untersuchungen über die interauriculäre Reizleitung, *Ztschr. f. d. ges. exper. Med.*, 1929, lxviii, 516-528.
13. GROEDEL, F.: Verdoppelung der Vorhofzacke des Elektrokardiogramms bei a-v Block die Folge einer Längsdissoziation der Vorhöfe, oder Darstellung der Vorhofenzacke? *Verhandl. d. deutsch. Ges. f. inn. Med.*, 1921, 494.
14. TRENDELENBURG, W.: Untersuchungen über die Aktionsströme des menschlichen Herzens. II. Mitt. Ueber die Vorhofschwankung P des Elektrokardiogramms, *Ztschr. f. d. ges. exper. Med.*, 1934, xcii, 20-29.
15. v. BOROS, J.: Ueber die Formveränderungen des Elektrokardiogramms infolge vorübergehender Leitungsstörung, *Wien. Arch. f. inn. Med.*, 1930, xix, 338-350.
16. LAUFER, S.: Dérivations electives des oreillettes dans le diagnostic des troubles de la fonction auriculaire, *Arch. d. mal. du coeur*, 1935, xxviii, 98-101.
17. LAUFER, S., and RUBINO, A.: Sull' importanza delle derivazioni elettive nella diagnosi dei disturbi di conduzione del miocardioatriale, *La clin. med. ital.*, 1936, lxvii, 363-381.
18. ROTHBERGER, C. J.: Normale und pathologische Physiologie der Rhythmik und Koordination des Herzens, *Ergebn. d. Physiol.*, 1931, xxxii, 472-820.
19. MAHAHM, I.: De l'anévrysme primitif de l'oreillette gauche. Troubles particuliers du rythme cardiaque. La dissociation interauriculaire, *Ann. de méd.*, 1927, xxi, 380-409.

LYMPHANGITIC CARCINOMATOSIS OF THE LUNGS; CASE
REPORT WITH AUTOPSY FINDINGS *

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INFILTRATION of the pleural, peribronchial, and perivascular lymphatics by neoplastic cells is a condition first noted by Andral¹ in 1829, again by Virchow² in 1855 and of which the gross lesions and the histopathology were described in detail by Troissier³ and Raynaud⁴ in 1874. It is most commonly secondary to carcinoma of the stomach, usually of the scirrhus infiltrating type, but primary sites in the bronchus and breast,⁵ rectum,⁶ kidney,^{7,8} ovary,⁹ tongue,¹⁰ prostate¹¹ and liver,¹² have been noted. The primary gastric malignancy is often clinically latent, or causes few symptoms, and the presenting complaints are those of respiratory or circulatory embarrassment. In some of the reported cases there has occurred bone marrow involvement with a clinical picture predominantly that of a blood dyscrasia. In others, typical Krukenberg tumors have been found and, in these, the primary clinical manifestations are often referable to the pelvis.

CASE REPORT

A colored male, aged 37, was admitted to the hospital with a complaint of left-sided chest pain, cough, hemoptysis and fever. The onset of the complaint was about three months before admission at which time there was noted a dull ache in the left thorax, which was exaggerated by coughing. Cough was not persistent until about three weeks before admission when it became severe, and was accompanied on each occasion by expectoration of about a teaspoonful of purulent material tinged with blood. Dyspnea on exertion appeared at about this time. During the previous two months there had been an evening rise in temperature. There had been considerable loss of weight. The past history was insignificant except for the presence of occasional gaseous distention and vague epigastric pain. Gonorrhea and syphilis had been contracted two years before admission.

Physical examination showed a well-developed, well-nourished, colored male with a blood pressure of 135 mm. of Hg systolic and 95 mm. of Hg diastolic, a pulse rate of 110 per minute and "a rapid rate of respiration." There was a scar on the right side of the neck said to have been caused by a "gland breaking down and draining from 1918 to 1924." There was lagging and limitation of motion of the left upper thorax. Fine râles, increased fremitus, and dullness on percussion were found in the left upper anterior and posterior portions of the chest. The rest of the physical examination was normal. The clinical impression was pulmonary tuberculosis versus pulmonary actinomycosis. The laboratory findings were as follows: Examinations of the sputum on eight different occasions, three of these being 24 hour concentrated specimens, were negative for acid fast organisms, nor were fungi found. Roentgenogram of the chest, on the day of admission, showed widely disseminated vesicular lesions in the middle areas of both lungs, and the left lower lung. The lesions were more or less discrete in the perihilar region, and in the left lower lung

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there was extensive lung reaction. It was thought that the changes were most likely due to actinomycosis or other mycotic infection, although the possibility of miliary carcinomatous metastases was mentioned.

An erect posterior-anterior roentgenogram the next day was interpreted as indicating tuberculous bronchopneumonia throughout both lungs. Approximately one month later a similar roentgenogram showed no further changes. Again, one month later (two months after the patient's admission) an erect posterior-anterior roentgenogram was taken and no change of the bilateral miliary disease was seen, but there was a complete clearing up of the large area of reaction in the left lower lung. It was here suggested that infestation with *Paragonimus westermanni* be considered, but sputum and stool examinations were negative for this parasite. The blood count of this time showed a hemoglobin of 30 per cent (Sahli), 8,000,000 red blood cells, of which many were immature forms, and a white cell total of 10,400. The differential count was normal. A blood Wasserman test was negative.

Course: The course was progressively down hill. The temperature ran a septic course, varying from 98° to 101° daily. The pulse rate changes were in accord with temperature changes and varied from 80 to 120 per minute. The respiratory rate, however, increased progressively from 20 per minute on admission to 45-50 per minute during the terminal weeks of the patient's illness. Fifteen days before the death of the patient, he raised about 50 c.c. of "Burgundy-red" fluid, which gave a strongly positive benzidine reaction, but was negative for organisms except spirochetes and streptococci. The dyspnea became so severe that morphinè was required to relieve the distress during the terminal month. The patient died two and a half months after admission, five and a half months after onset of symptoms, and no final clinical diagnosis was made.

Autopsy: Necropsy was performed 72 hours after death. The external examination, except for emaciation, was negative. The peritoneal cavity and abdominal organs were normal in appearance and relationship except for prominent lymphatic channels over the peritoneal surface of the diaphragm, and enlarged lymph nodes along the lesser curvature of the stomach. In addition a large mass involving the stomach wall was palpated; it extended from over the cardiac end of the stomach down to within 3 cm. of the pyloric sphincter along the lesser curvature. The wall of the stomach, particularly in the region of the lesser curvature, was quite indurated in the cardiac one third. The left pleural cavity was completely obliterated over the lower lobe. The pleura over the left lower lobe was markedly thickened, white in color, and areas of calcification were present. The visceral pleura over the left upper lobe showed marked distention of the lymphatics. The visceral pleura over the entire right lung showed a similar lymphatic distention. The cut surface of the lungs showed dilated lymphatics along the bronchial and vascular trees. A few small areas of bronchopneumonia were scattered throughout. The bronchial mucosa was congested, and some of the bronchi contained a hemorrhagic, purulent material. The tracheobronchial lymph nodes were not enlarged but, on section, showed white miliary nodules. The pleural surface of the diaphragm showed dilated lymphatics similar to those seen on the peritoneal surface.

The peripancreatic lymph nodes were enlarged, and on section were firm and had a white color. On opening the stomach, a large ulcerated mass along the entire course of the lesser curvature was found. In the cardiac area the tumor was firm in consistency and scirrhus in nature, and the mucosa was absent over this area. In the pyloric region the mass was polypoid and gelatinous in appearance. Radiating from this tumor there were dilated lymphatics, with nodules interspersed along their courses. The capacity of the stomach did not appear to be lessened.

The periaortic lymph nodes were enlarged and some were caseous. The heart was normal except for dilatation of all chambers and moderate atherosclerosis of the

mitral and aortic valves. A small white nodule 3 mm. in diameter was found in a medullary pyramid of the right kidney. The liver, gall-bladder and duct system, spleen, pancreas, intestinal tract, kidneys, adrenals, ureters, urinary bladder, and genitalia were otherwise grossly normal.

MICROSCOPIC EXAMINATION

Lung: The pleura showed an increased amount of connective tissue. There was more or less reduction of the size of the blood vessels due to intimal proliferation. Many of the adjacent lymphatic channels were widely dilated by plugs of neoplastic cells. These cells were large, had a pale cytoplasm, basophilic nuclei, and many showed mitosis. The majority of the smaller arterioles throughout the entire lung section showed a similar involvement. Masses of these tumor cells were also seen in the blood vessels of the alveolar septa. An occasional arteriole showed a recanalization of a thrombus, and tumor cells were seen in the newly formed channels. The alveolar spaces showed in some places an accumulation of fibrin and a few round cells. Otherwise they were normal. The bronchiolar and bronchial mucosa was normal.

Stomach: The mucosa was replaced by atypical glandular tubules which penetrated through the muscularis mucosae to the submucosa. These tubules were lined by several layers of cells with large hyperchromatic nuclei, the cytoplasm of which was pale and the borders indistinct. There was some myxomatous degeneration of the connective tissue of the submucosal layers.

Diaphragm: The lymph channels of the section showed a distention by tumor cells similar to the process seen in the pleura. Otherwise no abnormalities were present.

Periaortic Lymph Node: The architecture of the node had been greatly distorted because of replacement of normal tissue by neoplastic cells. These were large, had a pale cytoplasm, and deeply stained nuclei. Some showed mitosis. The capsule was thickened but did not appear to be invaded.

The heart, liver, spleen, adrenal glands, kidneys, prostate, and the remainder of the intestinal tract showed no unusual findings.

DISCUSSION

Because of the protean clinical manifestations, lymphangitic carcinomatosis of the lungs is usually diagnosed with more or less difficulty. In general it occurs most commonly in young adults—the great majority of cases occurring before the age of forty. As previously mentioned it is most frequently secondary to scirrhous carcinoma of the stomach. The primary gastric malignancy, which varies in size from a microscopic area^{13, 14, 15} to one, as in the present case report, involving a large portion of the stomach, is often clinically latent or causes few symptoms,^{16, 17, 18, 19, 20, 21} and the presenting complaints, as previously stated, are those of respiratory difficulty or circulatory embarrassment. The respiratory symptoms are rapidly progressing dyspnea with or without cyanosis,^{5, 16} a slight cough, the expectoration of a thin brownish, sometimes purulent or sanguineous, sputum. There is a rapid downhill course.²² The chest findings on examination are negative, or insignificant in proportion to the symptoms.^{23, 24} The roentgen-ray findings are often times suggestive, but are not diagnostic. The characteristic appearance is a markedly stringed design in both lungs, which consists of branching lines which arise from the hilum and break up into a fine network as they extend toward the periphery, and at the

points of intersection miliary nodules may be seen. Frequently the hilar nodes are enlarged.^{24, 25, 26, 27, 28} Right sided heart failure or asphyxia is not uncommonly the mode of exitus.^{5, 17, 20, 29, 30, 31}

The gross pathologic findings in the lungs are characteristic if sufficiently marked, but in some cases the nature of the pulmonary involvement has not been



FIG. 1. Distention of subpleural lymphatics. (From Textbook of Pathology, by C. W. Duval and H. J. Schattenberg, page 517, 1939, D. Appleton-Century Co., New York.)

suspected until microscopic examination has revealed its identity.^{5, 12, 14, 18, 21, 32, 33, 34, 35, 36, 37}

The lung is larger, firmer, and more moist than normal. There is a dilatation of the pleural lymphatic channels which causes them to stand out prominently, and the lobules of the lung are characteristically delineated. At the points of intersection of the lymphatic channels small yellowish white nodules may be seen (figure 1). On cut section the lung appears mottled and similar involvement of peribronchial and perivascular lymphatics is seen. Small plugs can be ex-

pressed sometimes from these involved vessels. Microscopically, tumor cells are found filling the perivascular, peribronchial, and pleural lymphatics (figures 2 and 3). In many cases, tumor cells are also found in the vessels of the alveolar walls (figure 4) and there is often noted an intimal proliferation, sometimes elliptical in nature,²⁹ which more or less occludes the arterioles (figure 5). Also there is occasionally thrombosis of a vessel with tumor cells present in the thrombus, and again recanalized thromboses are seen with tumor cells lying in the newly formed channels (figure 6).



FIG. 2. Section of pleura showing tumor cells lying in a lymphatic channel. ($\times 100$.)

The method of spread to the lung is, most probably, by retrograde lymphatic involvement, following lymphatic permeation^{26, 38, 39, 40, 41, 42} but the frequency with which tumor cells are found distending the channels of alveolar walls demands another explanation, since these are definitely blood, and not lymph, vessels.⁴³ In a case reported by Turettini and Gerber⁴⁴ there was thrombosis of the superior vena cava, right internal jugular vein, and the right axillary vein. In a case reported by Boccard³⁰ there was thrombosis of the left basilic and saphenous veins. Chylous ascites was present in Gamberini's case⁴⁵ and in a case reported by Poppi²⁸ there was also chylous ascites, as well as thrombosis of the left subclavian vein. These observations support the possibility that the thoracic duct is involved, and tumor cells gain entrance to the venous circulation in this way.³⁷

The presently described case is one in which the form of lymphangitic carcinomatosis is predominantly pulmonary in its clinical manifestations. There are several other ways in which a metastatic carcinoma infiltrating the pulmonary channels may first manifest itself. One of these is right-sided heart involvement. There is first hypertrophy and then dilatation. If dyspnea and cyanosis are also present, the condition may simulate Ayerza's disease. Montgomery⁴⁶ has suggested the use of the term "Ayerza's syndrome" and voices the opinion that while the clinical features are clear cut, the underlying pathological process may be quite different in individual cases.⁴⁷ The blockage of the pulmonary



FIG. 3. The lymph channels adjacent to an arteriole are plugged by tumor cells. There is intimal proliferation of the arteriole. ($\times 440$.)

circulation by the widespread intimal hyperplasia, arteriolar thromboses, and the further reduction of blood flow by the myriad tumor-cell emboli explains the hypertrophy of the right heart. The cyanosis and asphyxia are probably due to the reduction of pulmonary ventilating area,⁴⁸ although Porges, in discussing cases reported by Cérkake²³ attributed the dyspnea to stiffening of the lung by the carcinomatous infiltration of alveolar septa. Girode⁴⁰ believed that edema of the lung was the underlying factor. Von Meyenburg³⁹ felt that there was a cardiac element in his cases, and Goldmann⁴⁹ suggested that there was an intoxication of the nervous centers by the products of the neoplasm.

There have been a number of cases reported in which extensive bone marrow metastases were noted, as well as lymphatic infiltration of the lungs.^{11, 12, 14, 32, 34,}

^{35, 36, 50, 51, 52} The predominant clinical features of these cases were those of a blood dyscrasia. The blood changes subsequent to cancerous involvement of the bone marrow are known in the French literature as the syndrome of Weil and Clerc⁵⁴ and the principal manifestation is a hemorrhagic diathesis. The next commonest change, excluding anemia, is the presence of immature leukocytes and erythrocytes in the peripheral blood. Curiously enough, in a number of cases reported of lymphangitic carcinomatosis, a thrombocytopenia has been



FIG. 4. Infiltration of blood channels of alveolar septa by tumor cells. ($\times 900$.)

noted ^{11, 12, 14, 32, 34, 35, 52, 53} which is not in accord with the view that in carcinoma the platelets are normal, or increased in number in the circulating blood.^{55, 56, 57} Because of the lack of other symptoms, certain of these cases have been diagnosed as pernicious anemia, purpura, or leukemia,^{32, 35, 36} and an unsuspected lymphangitic carcinomatosis of the lungs secondary to a primary gastric malignancy was found at autopsy. The method of metastasis to the bone marrow is not as obvious as in the other related syndromes in which it is characteristically

lymphogenous. The consensus of opinion is that the bone marrow is not supplied with lymphatics, but certain experimental work⁵⁸ is suggestive of the presence of lymphatics in the bone marrow, and to be consistent in keeping with the tendency of this tumor to metastasize by the lymphogenous route, it might be expected that the bone marrow is thus involved.

Finally the high occurrence of the Krukenberg tumor in the reported cases of lymphangitic carcinomatosis of the lung may be of significance. The classical Krukenberg tumors of the ovary are now considered to be generally secondary to gastrointestinal carcinoma, and quite frequently secondary to gastric carcinoma.

Certain clinical features of Krukenberg tumor are interesting in connection

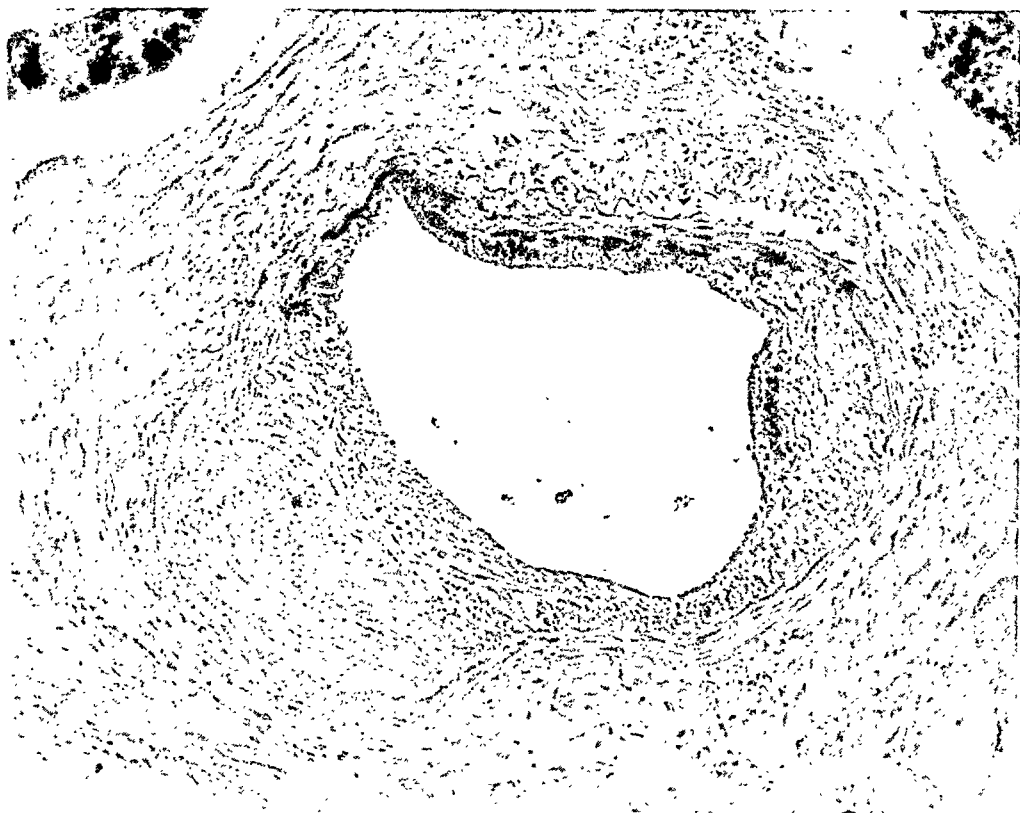


FIG. 5. Elliptical vascular intimal proliferation. ($\times 440$.)

with the occurrence of lymphangitic carcinomatosis of the lung. Krukenberg tumors tend to occur in young adults, and also the primary carcinoma is often clinically latent. The average age for malignant tumors of the ovary, primary or secondary (excluding cystic teratoma and possible sarcoma) falls between 42 and 50 years.⁵⁹ The average age of occurrence of Krukenberg tumor is well under this.^{60, 61, 62} The pelvic symptoms are frequently the first, and later developments of gastrointestinal, or pulmonary symptoms, follow, or the gastrointestinal involvement is an incidental finding at operation or autopsy.^{63, 64, 19} Of interest is one report⁶⁵ of a patient operated upon successively for adenocarcinoma of the stomach and Krukenberg tumor of the ovary, who then developed lymphangitic carcinomatosis of the lungs.

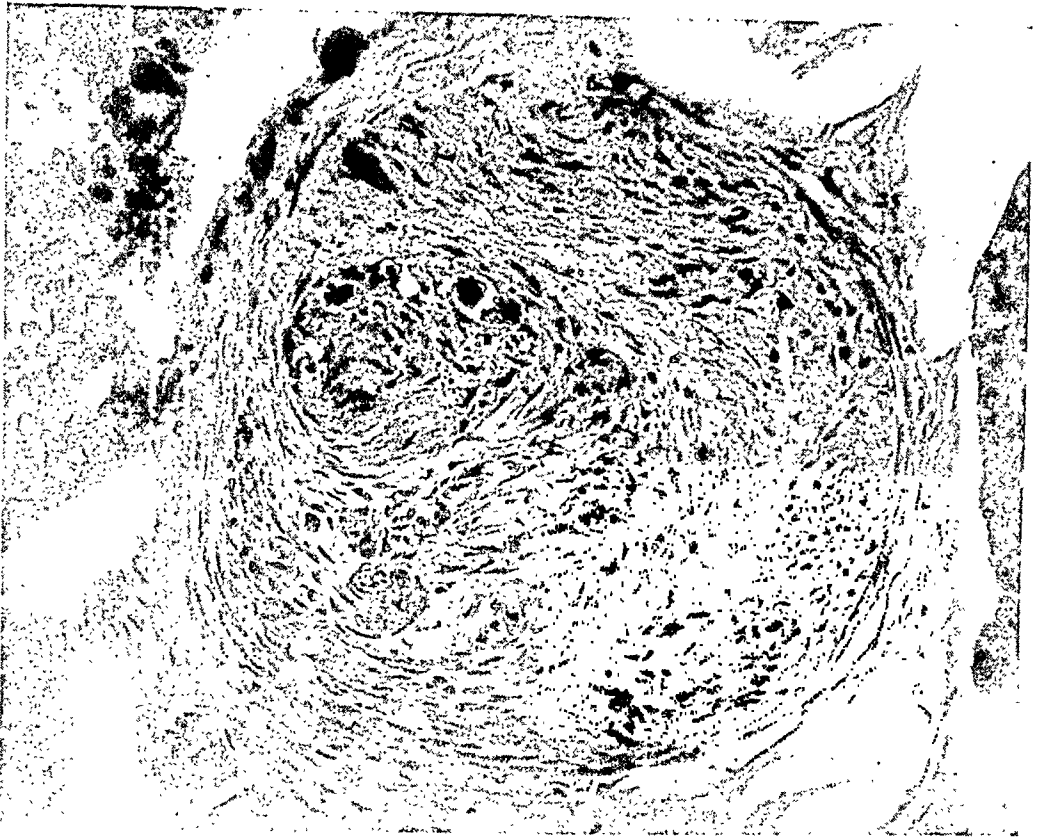


FIG. 6. Recanalized vessel with tumor cells in new channels. ($\times 900$.)

SUMMARY

Lymphangitic carcinomatosis of the lungs is not an uncommon form of metastasis in gastrointestinal carcinoma, especially scirrhus carcinoma of the stomach, in young individuals.

The symptoms and signs due to the lung involvement may be similar to, and must be differentiated from, Ayerza's syndrome, pulmonary tuberculosis, pulmonary fungus infection or pulmonary infestation by *Paragonimus westermani*.

Certain blood dyscrasias are noted at times in connection with lymphangitic carcinomatosis of the lungs and these may be due to metastatic involvement of the bone marrow.

A significant incidence of Krukenberg tumor of the ovary has been noted in cases of lymphangitic carcinomatosis of the lungs.

The signs and symptoms caused by the metastatic foci often overshadow those of the primary lesion, or the primary lesion may be clinically latent.

REFERENCES

1. ANDRAL, G.: Précis. de path. Anat., Paris, 1829, ii, 44.
2. VIRCHOW, R.: Gaz. Méd., 1855, 211. Quoted by Troissier and Wu.
3. TROISSIER, E.: Cancer de l'estomac; Cancer secondaire des poumons. Lymphangite pulmonaire généralisée, Bull. Soc. Anat. de Paris, 1873, xlviii, 834. Ibid: Recherches sur la lymphangite pulmonaire, Thèse de Paris, 1874, 142.

4. RAYNAUD, M.: Lecture d'une mémoire sur l'angioleucite généralisée des poumons, *Bull. et mém. soc. méd. de hôp. de Paris*, 1874, xi, 66.
5. WU, T. T.: Generalized lymphatic carcinosis (lymphangitis carcinomatosa) of the lungs, *Jr. Path. and Bact.*, 1936, xliii, 61-76.
6. EIZAGUIRRE, L.: Diffuse hematogenous metastases in lungs secondary to carcinoma of rectum, *Arch. de med. cir. y. especialid*, 1935, xxxviii, 153.
7. LEVAI, G.: Miliary carcinosis of lungs originating from carcinoma of kidney, *Magyar orvosi arch.*, 1927, xxviii, 161.
8. BABES, A., and STOIA, I.: Renal adenocarcinoma with multiple metastases of lungs and cranial skin, *Bull. et mém. soc. méd. d. hôp. de Bucharest*, 1928, x, 271.
9. MORETTI, E.: Generalized lymphatic carcinosis of lungs secondary to ovarian cancer, *Rev. di. clin. med.*, 1933, xxxiv, 639.
10. EWING, J.: Neoplastic diseases, third edition, 1928, W. B. Saunders Co., Philadelphia, p. 890.
11. COHEN, JOHAN: Blood picture in metastatic cancer of bone marrow, *Nederl. tijdschr. v. geneesk.*, 1929, lxxiii, pt. 2, 5485-5487.
12. HERZOG, F., and ROSCHER, A.: Beiträge zur Pathologie der Thrombopenie, *Virchow's Arch. f. path. Anat.*, 1921, ccxxxiii, 347-371.
13. TERPLAN, K., and SOMMER, G.: Ueber ein bei der Sektion mit freiem Auge unerkant gebliebenes diffuses Karzinom des Magens, *Beitr. z. path. Anat. u. z. allg. Path.*, 1931, lxxxvii, 229.
14. TERPLAN, K., and VAUGHN, S. L.: Primary carcinoma of the stomach grossly unrecognized—with extensive metastases to the bone marrow producing marked intravital erythroblastosis, *Arch. Path.*, 1934, xviii, 924.
15. SIMECEK, A.: Diagnosis of Krukenberg tumor, *Am. Jr. Cancer*, 1937, xxxi, 21-27.
16. DESBUQUOIS, G.: Miliary carcinoma of lungs secondary to latent carcinoma of stomach, *Bull. et mém. soc. de méd. d. hôp. de Paris*, 1935, li, 1420.
17. ACHARD, C., BARIETY, M., DESBUQUOIS, G., and STERNFELD: Miliary carcinosis of lung secondary to latent gastric carcinoma, *Bull. et mém. soc. méd. d. hôp. de Paris*, 1931, xlvii, 184.
18. FREEZOR, C. R. E.: A case of latent carcinoma ventriculi with extensive skin metastasis, *Guy's Hosp. Rep.*, 1927, lxxvii, 222.
19. CURPHEY, W. C.: Hypernephroma of kidney and carcinoma of stomach obscured by metastases, Case No. 2, *Jr. Kansas Med. Soc.*, 1932, xxxiii, 452-453.
20. GAINES, L. M.: Diagnostic problem of causation of dyspnea, report of case with autopsy, *Jr. Am. Med. Assoc.*, 1935, civ, 632.
21. CABOT Case No. 16182, *New Eng. Jr. Med.*, 1930, ccii, 881-882.
22. COLLIN, M.: *Presse med.*, 1921, xxix, 20. Quoted by Jarcho, S.
23. CÉRKAKE, P.: *Klin. Wchnschr.*, 1922, i, 1027. Quoted by Jarcho.
24. DALLA VOLTA, A., and VALENTI, A.: *Arch. di pat. e clin. med.*, 1923, ii, 568. Quoted by Jarcho.
25. LORENZ, H.: *Fortschr. a. d. Geb. d. Röntgenstr.*, 1921-1922, xxviii, 430. Quoted by Wu.
26. SCHWARZMANN, A.: Über generalisierte carcinomatöse Lymphangitis der Lungen, *Acta Radiol.*, 1934, xv, 491.
27. ASSMAN, H.: *Klinische Roentgendiagnostik der innern Erkrankungen*, third edition, 1924, F. C. W. Vogel, Leipzig, p. 314.
28. POPPI, A.: Generalized endolymphatic pulmonary carcinosis; clinical, radiological and pathological study, *Arch. di pat. e clin. med.*, 1935, xiv, 487.
29. GREENSPAN, E.: Carcinomatous endarteritis of the pulmonary vessels resulting in failure of the right ventricle, *Arch. Int. Med.*, 1934, liv, 625-644.
30. BOCCARD, A.: La forme asphyxiante aiguë de la carcinose secondaire du poumon, *Thèse de Paris*, 1925, 236.

31. COSTEDOAT, A., and CODVILLE, F.: Granulie cancéreuse des poumons chez un tuberculeux opéré huit ans auparavant d'un cancer gastrique, *Bull. et mém. soc. méd. d. hôp. de Paris*, 1932, xlviii, 1159.
32. SEEMANN, G., and KRASNOPOLSKI, A.: Akute "Leukanämie" mit starker extramedullärer Blutbildung als Folge ausgedehnter Knochenmarksverdrängung durch Magenkrebsmetastasen, *Virchow's Arch. f. path. Anat.*, 1926, cclxii, 697.
33. LENOIR and COURCOUX: Septicémie cancéreuse secondaire, *Presse méd.*, 1908, xvi, 757.
34. LAWRENCE, J. S., and MAHONEY, E. B.: Thrombopenic purpura associated with carcinoma of the stomach with extensive metastases, *Am. Jr. Path.*, 1934, x, 383-390.
35. STEBBINS, G. C., and CARNS, M. L.: Thrombocytopenic purpura associated with adenocarcinoma of the stomach in a young adult, *Arch. Path.*, 1935, xx, 247-252.
36. COPELAND, M. M.: Skeletal metastases arising from carcinoma and from sarcoma, *Arch. Surg.*, 1931, xxiii, 581.
37. SCHMIDT, M. B.: Ueber Krebszellenembolien in den Lungenarterien, *Verhandl. d. deutsch. naturforsch. Braunschweig*, 1897, xv, 11. *Ibid*: Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarcome zu den leukaemischen Neubildungen, 1903, G. Fischer, Jena.
38. HANDLEY, W. S.: The dissemination of mammary carcinoma, *Lancet*, 1905, i, 983-986.
39. VON MEYENBURG, H.: Zur Kenntnis der Lymphangitis carcinomatosa in Lungen und Pleura, *Cor.-Bl. f. schweiz. Aerzte*, 1919, xlix, 1668.
40. GIRODE, J.: Lymphangite cancéreuse pluro-plumonaire sans cancer du poumon, *Arch. gén. de méd.*, 1889, i, 50.
41. LE COUNT, E. R.: The genesis of carcinoma of the fallopian tube in hyperplastic salpingitis, with report of a case and a table of twenty-one reported cases, *Bull. Johns Hopkins Hosp.*, 1901, xxxii, 55-68.
42. COSTEDOAT, A.: La lymphangite cancéreuse des poumons, *Presse méd.*, 1933, xli, 745-748.
43. MILLER, W. S.: *The lung*, 1937, Chas. C. Thomas, Springfield, Illinois and Baltimore, Md., p. 90.
44. TURETTINI, G., and GERBER, I.: Pulmonary lymphangitis from gastric cancer, *Rev. Med. de la Suisse Rom.*, 1920, xl, 177.
45. GAMBERINI, M.: Carcinosi generalizzata linfangitica pleuropolmonare, *Policlinico (sez. med.)*, 1928, xxxv, 493.
46. MONTGOMERY, G. L.: Case of pulmonary artery thrombosis with Ayerza's syndrome, *Jr. Path. and Bact.*, 1935, xli, 221.
47. MUSSER, J. H.: *Internal medicine*, third edition, 1938, page 781, Lea & Febiger, Philadelphia, Pa.
48. BARD, L.: La lymphangite pulmonaire cancéreuse généralisée, *Semaine méd.*, 1906, xxvi, 145.
49. GOLDMANN, L. N.: Zur klinischen Symptomatologie der lymphangitis carcinomatosa der Lungen und Pleura, *Ztschr. f. Krebsforsch.*, 1931, xxxiv, 405.
50. EPSTEIN, J.: Blutbefunde bei metastatischer Carcinose des Knochenmarkes, *Ztschr. f. klin. Med.*, 1896, xxx, 121-128.
51. FRESE, O.: Ueber schwere Anämie bei metastatischer Knochencarcinose und über eine "myeloide Umwandlung" der Milz, *Deutsch. Arch. f. klin. Med.*, 1900, lxviii, 387.
52. STILLMAN, RALPH G.: Coincidence of malignant tumor and purpura hemorrhagica (Case 2), *Med. Clin. N. Am.*, 1930-31, xiv, 1533-1538.
53. JARCHO, S.: Correlation of several varieties of tumor metastasis, *Arch. Path.*, 1936, xxii, 674-696.
54. WEIL, P., and CLERC, A.: La splénomégalie chronique avec anémie et réaction myéloide du sang, *Semaine med.*, 1902, xxii, 373.
55. HAYEM, G.: *Du sang et ses alterations anatomiques*, 1889, G. Masson, Paris.
56. NAEGELI, O.: *Blutkrankheiten und Blutdiagnostik*, 1931, Julius Springer, Berlin, p. 661.

57. MORRISON, MAURICE: Analysis of blood picture in 100 cases of malignancy, Jr. Lab. and Clin. Med., 1931-32, xvii, 1071-1093.
58. KOLODNY, A.: Relation of bone marrow to lymphatic system, Arch. Surg., 1925, xi, 690.
59. BELL, W. B., and DATNOW, M. M.: Ovarian neoplasms; some points in their pathology, clinical features and treatment, Am. Jr. Cancer, 1932, xvi, 1, 439.
60. KRUKENBERG, F.: Über das Fibrosarcoma ovarii mucocellulare (Carcinomatodes), Arch. f. Gynäk., 1895, I, 287.
61. VAPTZAROFF, Y. D.: Contribution à l'étude des "tumeurs de Krükenberg," Bordeaux Thesis, 1934.
62. JARCHO, J.: Further studies of the Krukenberg tumor of the ovary, Am. Jr. Surg. (N.S.), 1938, xli, 537.
Idem: Krukenberg tumors and their practical problems, Am. Jr. Obst. and Gynec., 1927, xiii, 288.
63. ESAU, A.: Krukenbergtumoren in der Schwangerschaft. Nachtrag zu der Arbeit von Dr. Puppel, Zentralbl. f. Gynäk., 1933, lvii, 1167.
64. FRANSSEN, R.: Un pseudo-oophoroma de l'ovaire metastase d'un cancer intestinal, Ann. d'anat. path., 1930, vii, 1053.
65. CLERENS, J.: A propos d'un cas de tumeur de Krukenberg, Jr. de chir. et ann. soc. belge de chir., 1938, xxxvii, 47-48.

EDITORIAL

THE AMERICAN COLLEGE OF PHYSICIANS AND MEDICAL DEFENSE

IN THE Defense Program in which this Nation is engaged, a heavy responsibility falls upon the medical profession. The efficiency of the Army and of the Navy in this period of rapid growth depends to a marked degree upon the careful selection of those young men best fitted by physique and mentality to meet the requirements of active service in war. It depends equally upon the maintenance in vigorous health of those already inducted who in camps and at sea are being moulded into a force prepared to meet any challenge. These young soldiers and sailors and aviators, so history teaches us, if it were not for modern medical care would suffer in this training period a rate of disability and death from disease quite comparable to the casualty rate in active combat. To safeguard our growing defense forces involves a major medical program which both in its planning and in its execution calls for the services of the ablest men in the medical profession. Moreover since the medical personnel which will serve these new military forces must be drawn to a great extent from the ranks of medical men now in civilian practice it is necessary that they be so selected as not to reduce the number of practitioners in any area below the minimum required to meet the civilian needs for medical care. Our rural and urban districts must retain a sufficient number of physicians, our hospitals and dispensaries must continue to function, and our medical schools must be able to ensure a continuing flow of well-trained young graduates. It must be expected that when the Army and Navy have taken their quota, the remaining physicians will bear their share of the burden of adequate defense through the longer hours of work that will be required of them.

The profession as a whole then will be called to the service of the nation as it has been in all past war emergencies. No group will fail to do its share. Each, however, has the right to take pride in the part played by its members.

It is for this reason and to make some record, partial though it must be, of what part members of the American College of Physicians are taking in this present phase of the Defense Program that this brief summary is presented.

In the regular Medical Corps of both the Army and Navy the American College of Physicians has many members and both Surgeon General Magee of the Army and Surgeon General McIntire of the Navy, as well as Surgeon General Parran of the Public Health Service, are Fellows of the College.

An unknown but large number of the members of the College are officers of the Medical Reserve Corps. Many of these are now being called into active service chiefly to man the medical divisions of cantonment hospitals. Many other members have joined the Reserve to aid in filling medical divi-

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5. On Surgical Infections. Chm. Dr. F. L. Meleney.
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| e. On Ophthalmology. | Dr. Gradle. |
| f. On Neuro-Surgery. | Dr. Naffziger. |
| g. On Facio-Maxil. Surgery. | Dr. Ivy. |
| h. On Oto-Laryngology. | Dr. Mosher. |

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VI. Committee on Aviation Medicine. Chm. Dr. DuBois.*

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4. On Personnel. Chm. Dr. Steckel.

sions of General Hospitals now being organized by Medical Schools for service in case of war.

Another large unlisted group of College members have accepted appointment and are hard at work on local Draft Boards, Advisory Boards and Induction Boards. Aside from those called into active service no other physicians have taken on such onerous duties for their country's defense as these men and all other physicians on these Boards.

The College is proud too of those of its membership who, working under the aegis of the Committee of Medical Preparedness of the American Medical Association, are engaged in every state in the difficult task of assisting the Army in the selection of medical officers in a way which will least affect the efficiency of medical practice, medical institutions and medical schools.

Likewise our members have been called to assist in the medical aspects of the work of the State Defense Councils.

Early in the development of the Defense Program the Surgeons General of the Army and Navy called upon the National Research Council to mobilize through its Division of Medical Sciences authoritative medical advice for the Medical Corps in purely professional subjects. The way in which this task has been performed is graphically shown in the adjoining chart.* It must prove a source of gratification to all the College to note how many of its Fellows have been honored by inclusion in these advisory bodies. As a result of the work of these Committees many research projects are underway, manuals are being written and far-reaching plans worked out to meet future possible eventualities.

In this connection the Regents of the College took official action in December in making available an emergency fund to the Executive Committee from which the Medical Committee of the National Research Council might obtain financial help for an urgent need which could not be met through the slow process of a special governmental appropriation. This fund stands as an evidence of the attitude of the College which was expressed by President Bruce when last fall he formally offered to the Government the services of the American College of Physicians in the Defense Program. As individuals and as a College our members have a right to pride in the part they have already played. The future shall not find us lacking.

* Since this organization is in process of growth, omissions or minor errors may be present in the chart.

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D. David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. 1940 Supplement. xxxvii + 771 pages; 25 × 17.5 cm. D. Appleton-Century Company, Inc., New York. 1941. Price, \$10.00.

As they have appeared in the interval between 1932 and 1938, the thirteen preceding volumes of *The Practitioner's Library of Medicine and Surgery* have been briefly described in the ANNALS. In order to keep this work abreast of the recent significant advances in Medicine a *1940 Supplement* has been published. In its 64 chapters by almost as many authors, new disease entities are discussed and new diagnostic and therapeutic technics are described. The arrangement of the chapters in this volume follows in general that of the *Library* as a whole. Among the topics presented are the medical applications of neutron rays and artificial radioactivity, the modern hypothesis and the clinical aspects of the menstrual cycle, the pneumococcus, diagnostic roentgenology with special reference to the newer technics, technic and indications for the use of gastroduodenal aspiration, equine encephalitis, acute interstitial pneumonia, rickettsioses, epulis granulomatosa, acute disseminated lupus erythematosus, torulosis, toxoplasmic encephalomyelitis, histoplasmosis of Darling, tick paralysis, marihuana addiction, endemic dental fluorosis, cardiac contusion, leukemoid reactions, sulfanilamide and allied drugs, chemotherapy of gonococcal infections, the treatment of meningococcal infections and of lymphogranuloma venereum, gold therapy in chronic arthritis, indications for the use of vitamin K, the vitamin B deficiencies, the treatment of myasthenia gravis, dilantin sodium in epilepsy, recent progress in ophthalmology and in otology, and the end results of the toxemias of pregnancy. Other chapters, which cannot be listed here, cover material of equal interest and value. On the whole, the choice of subject material seems to be excellent. Obviously no attempt can be made to review the material of the individual articles in a collected work of this nature. There is a separate index as well as a detailed table of contents. The style and binding are uniform with those of the earlier volumes. As a well-planned addition to the *Library*, the *1940 Supplement* will be welcomed by all who use this medical encyclopedia.

C. V. W.

A Text-Book of Psychiatry. By D. K. HENDERSON, M.D., and R. D. GILLESPIE, M.D. Fifth Edition. 660 pages; 22.5 × 14.5 cm. Oxford University Press, London: Humphrey Milford. 1940. Price, \$6.00.

Since the first edition of this textbook was published in 1927, serious students of psychiatry have been indebted to these authors for the scholarly way in which the subject matter has been presented. The subsequent editions have lost none of this but rather have added timely, new material at the same high level.

The present edition is especially to be welcomed for certain important additions and changes. Particularly to be commended is the well balanced, critical presentation of the various shock therapies, together with a fair evaluation of their merits and disadvantages. The discussion of Gjessing's investigations of metabolic differences among the stuporous patients is also of interest.

The "boldness" of the authors in separating the psychopathic states from the mental defectives seems to be only in line with the present-day American trends. In the text it is more than justified by the result, for this section of the book is handled

much better than in earlier editions. The chapter on the psychiatry of childhood has benefited greatly by the additional material.

In general it may be said that, with the exception of what seems to the reviewer somewhat inadequate presentations on the subjects of electro-encephalography, details of the technic of the treatment of general paresis, and the clinical management of alcoholic intoxications, this text gives a highly satisfactory survey of the field of psychiatry. In no other text are the varied and at times conflicting theories discussed with so little bias. The authors let the various sources speak for themselves and the quotations and condensations from the literature are accurate.

The reviewer considers this the textbook of preference for serious students of psychiatry and psychiatrists.

L. F. W.

The Head and Neck in Roentgen Diagnosis. By HENRY K. PANCOAST, M.D., EUGENE P. PENDERGRASS, M.D., and J. PARSONS SCHAEFFER, M.D., PH.D. 976 pages; 26 × 18 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, \$12.50.

This is a one volume publication intended primarily for the roentgenologist; it covers thoroughly roentgenology of the head and neck. It is well printed and contains 1251 illustrations, the reproductions of the roentgen-ray films being of the best quality. A complete bibliography is appended which is a very valuable feature. An excellent subject index is likewise provided. Clearness and orderliness throughout the text are to be commended. In the preface the authors state "in order that maximal results in medical and surgical diagnosis by means of the roentgen-rays may be obtained, the basic and technical aspects of radiology must be correlated and integrated intimately with developmental and adult morphology, physiology, pathology and observations in clinical medicine and surgery and the special branches." This they have accomplished exceptionally well.

This book is divided into 12 chapters. The first chapter is devoted to the anatomy of the skull principally as seen radiographically with due attention given to the related structures and development. Variations and anomalies are considered in the general discussion as well as in a special section where they are described more fully. Chapter 2 deals with fractures of the skull and cervical spine. Fractures of the facial bones are considered individually. Great stress is placed upon doing a complete examination. The technic required to best demonstrate lesions is discussed.

Diseases of the bones (skull and cervical spine) and tumors of the scalp and cervical spine are described at length in chapters 3 and 4. Chapter 5 is devoted entirely to the teeth and jaws. The nose, lacrimal passage-ways, paranasal sinuses and temporal bones with special reference to the mastoids and petrous portions receive equal consideration in chapters 6 and 7.

There is an excellent chapter on intraorbital and intraocular foreign bodies. The authors describe the structural aspects of the eyeball in detail followed by the various roentgenographic methods of localization of foreign bodies. The modified Sweet method is discussed thoroughly.

Two especially interesting chapters are devoted to intracranial tumors and cerebral pneumography. The remainder of the book is taken up with chapters giving in detail roentgenographical diagnosis as applied to the neck.

This is an excellent and practical book which should be in the hands of every roentgenologist.

H. J. W.

Physical Diagnosis. By RALPH H. MAJOR, M.D. 464 pages; 24.5 × 16 cm. W. B. Saunders Co., Philadelphia. 1940. Price, \$5.00.

This is an interesting but somewhat disappointing textbook, couched in a moderately classical style with many Greek derivations and much historical lore.

After an interesting chapter on pain and the usual stressing of routine, there are excellent discussions of physical diagnosis as applied to the cardiovascular and respiratory systems. Other chapters are less adequate.

There is an abundance of pictures, many of them so extreme as to suggest Gould and Pyle rather than anything to be met with in ordinary student experience. None of the illustrations are in color, and where black and white photographs are used in an attempt to show comparison of color, as in Addison's disease, the effort is not felicitous. Diagrams and schematic presentations where used are very helpful and should be used more.

The rather general omission of vitamins in physical diagnosis is striking. Pellagra is mentioned, and scurvy, but so many of the other vitamin manifestations are omitted as to give the reviewer a feeling that they have been ignored entirely.

Occasional dicta are misleading, as where loss of hair and furrowing in the nails are ascribed specifically to typhoid fever instead of being part of many febrile and trophic disturbances. Coilonychia is beautifully illustrated, but ascribed entirely to pernicious anemia, instead of hypochromic anemias. Rhagades is attributed exclusively to syphilis, with no mention of the fact that it occurs in people who do not wear their dentures well. Elevation of temperature is described as characteristic of hemorrhage, without mention of time relation or whether the hemorrhage is internal or external.

The textbook has many good points, but because of the general lacks mentioned above is rather disappointing.

C. A.

Selected Writings of Sir Charles Sherrington. Compiled and edited by D. DENNY-BROWN. xiv plus 532 pages, with 85 diagrams; 26 × 18.5 cm. Paul B. Hoeber, Inc., New York. 1940. Price, \$7.50.

This book is comprised of extracts and reprints of many of the papers of Sir Charles Sherrington, and is a worthy tribute to his genius and versatility. The papers are not arranged chronologically but according to subject matter. The author has divided the book into 11 chapters which deal with the distribution of motor and sensory nerve roots, sensory nerves to muscles, the spinal animal and the nature of spinal reflex activity, features of spinal and bulbar reflexes, the anatomical course of reflex connections in the spinal cord, reciprocal innervation, postural reflexes, the motor area of the cerebral cortex, the nature of excitation and inhibition, and the quantitative management of contraction in lowest level coördination.

The book has a particular value from the arrangement of the material which has been well handled and illustrated, and it will be particularly useful as a reference book to the neurologist and physiologist.

A complete bibliography of Sir Charles Sherrington's writings is appended.

E. F. C.

COLLEGE NEWS NOTES

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Harry L. Arnold, Honolulu, T. H.
Dr. Paul W. Clough, Baltimore, Md.
Dr. Eugene Henry Drake, Portland, Maine
Dr. C. J. Fishman, Oklahoma City, Okla.
Dr. Russell Richardson, Philadelphia, Pa.
Dr. E. Sanborn Smith, Kirksville, Mo.
Dr. Edward L. Whitney, Walla Walla, Wash.
Dr. John R. Williams, Rochester, N. Y.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—1st Supplement to "Modern Drug Encyclopedia and Therapeutic Guide," 2nd edition;
Dr. Alpheus F. Jennings, F.A.C.P., Detroit, Mich.—"Typhoid Fever," reprinted from Tice's Practice of Medicine, Volume IV;
Dr. Solomon Solis-Cohen, F.A.C.P., Philadelphia, Pa.—"Judaism and Science";
Dr. J. Russell Twiss, F.A.C.P., New York, N. Y.—"Diagnosis and Management of Diseases of the Biliary Tract."

Reprints

Dr. J. Graham Bruce (Associate), Springfield, Mass.—1 reprint;
Rear Admr. Charles S. Butler, F.A.C.P., (MC), U.S.N., Retired, Bristol, Tenn.—1 reprint;
Dr. Hugh R. Butt, F.A.C.P., Rochester, Minn.—1 reprint;
Dr. J. William Finch (Associate), Hobart, Okla.—2 reprints;
Dr. Max L. Garon, F.A.C.P., Louisville, Ky.—1 reprint;
Dr. Vincent W. Koch, F.A.C.P., Janesville, Wis.—1 reprint;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Willard Machle (Associate), Cincinnati, Ohio—2 reprints;
Dr. Charles F. Nichols, F.A.C.P., Philadelphia, Pa.—2 reprints;
Dr. Dwight O'Hara, F.A.C.P., Boston, Mass.—1 reprint;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—2 reprints;
Dr. Zolton T. Wirtschafter (Associate), Cleveland, Ohio—2 reprints.

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows: For further details and application forms communicate with the respective secretaries.

American Board of Internal Medicine:

William S. Middleton, M.D., Secretary
1301 University Ave.
Madison, Wis.

American Board of Pathology:

F. W. Hartman, M.D., Secretary
Henry Ford Hospital
Detroit, Mich.

American Board of Pediatrics:

C. A. Aldrich, M.D., Secretary
707 Fullerton Ave.
Chicago, Ill.

American Board of Radiology:

B. R. Kirklin, M.D., Secretary
102 Second Ave., S. W.
Rochester, Minn.

Oral Examination, Boston, April, 1941,
in connection with meeting of the
American College of Physicians.

Oral Examination, Cleveland, June,
1941, in connection with meeting
of the American Medical Association.

Written Examination, October 20,
1941. Final date for filing application
is September 1, 1941.

Cleveland, June 2-3, 1941, in connection
with the meeting of the
American Medical Association.
Final date for filing application is
May 1, 1941.

New York City, March 30-31, 1941,
immediately following the Region
I meeting of the American Academy
of Pediatrics.

Chicago, May 18, 1941, immediately
following the Region III meeting
of the American Academy of
Pediatrics.

Boston, October 12, 1941, immediately
following the annual meeting of
the American Academy of Pediatrics.

Oral Examination, Cleveland, May 30-
June 1, 1941, in connection with
the meeting of the American
Medical Association. Final date
for filing application is April 15,
1941.

REGIONAL MEETING, FELLOWS AND ASSOCIATES OF EASTERN PENNSYLVANIA

Under the governorship of Governor Edward L. Bortz, the "Third Annual Round-Up" of Fellows and Associates of the American College of Physicians from Eastern Pennsylvania was held in Philadelphia, Friday, February 7, 1941. In addition to the members from Eastern Pennsylvania, Fellows and Associates from Delaware and southern New Jersey were invited, and several members from the western Pennsylvania district also were present. More than 200 members were in attendance.

The meeting started with a buffet luncheon at the College home, 4200 Pine Street, at one o'clock p.m. It was followed by a scientific program in the Clinical Amphitheater of Jefferson Medical College, as follows:

1. Clinic: "Viruses."

DR. HOBART A. REIMANN, Professor of Medicine, Jefferson Medical College,
Philadelphia.

2. "Gonadal Hormones."

DR. ROLAND KLEMMER, Chief of Medical Service, Lancaster General Hospital,
Lancaster.

3. "Emotional Growth."

DR. FRANCIS J. BRACELAND, Associate Professor of Clinical Psychiatry, Woman's Medical College; Assistant Professor of Psychiatry, University of Pennsylvania Graduate School of Medicine.

4. "Atelectasis."

DR. DONALD R. FERGUSON, Clinical Professor of Medicine and Visiting Physician, Hahnemann Medical College and Hospital.

5. "Arterial Hypotension."

DR. THOMAS M. DURANT, Associate Professor of Internal Medicine, Temple University School of Medicine.

6. Clinic: "Modern Therapy."

DR. HENRY K. MOHLER, Dean and Prevost Professor of Therapeutics, Jefferson Medical College.

The evening was given over to dinner and social activities. Dr. George Morris Piersol, Secretary-General, and former President of the College, was the toastmaster. Among special guests were the following College Governors: Dr. Charles F. Tenney, Governor for Eastern New York; Dr. Lewis B. Flinn, Governor for Delaware; Dr. Louis Krause, Governor for Maryland; Dr. Alex. M. Burgess, Governor for Rhode Island. Among other guests at the Speakers' Table were: Dr. Sidney R. Miller, Baltimore, former President of the College; Dr. Hubley R. Owen, Director of Public Health of Philadelphia; Dr. Margaret D. Craighill, Dean of the Woman's Medical College of Pennsylvania; Dr. William A. Pearson, Dean of Hahnemann Medical College of Philadelphia; Dr. Hobart A. Reimann, Professor of Medicine at Jefferson Medical College; Dr. George Muller, Philadelphia, former President of the American College of Surgeons; Dr. F. F. Borzell, President of the Medical Society of the State of Pennsylvania; Dr. O. H. Perry Pepper, Philadelphia, former President of the College; and Mr. E. R. Loveland, Executive Secretary of the College.

Dr. Pepper gave an address on the activities of the Committee on Medicine of the National Research Council, of which he is the Chairman, and of which the personnel is made up completely of Fellows of the College. The Committee on Medicine is conducting an important work in medical national defense, in an advisory capacity with the Surgeons-General of the Army and Navy. The Executive Secretary, Mr. Loveland, reviewed the progress of the College during the past fifteen years, and discussed the program of the forthcoming Annual Session of the College in Boston. Dr. Bortz made some remarks as the College Governor, but devoted most of his address to a discussion of the program of Postgraduate Courses for the current year, Dr. Bortz being the Chairman of the Advisory Committee on Postgraduate Courses. He pointed out that the registration to February 7 for the 1941 Courses, although many courses were not scheduled to start for six weeks thereafter, already had excelled the total registration of any preceding year. He especially commended to the physicians present Postgraduate Course No. 10, Military Medicine, arranged through the Public Services of the United States at Washington, April 7-18.

Short addresses were made or greetings extended by the other guests. Dr. Harry Wilmer, F.A.C.P., Philadelphia, and a number of his fellow members of the Orpheus Club of Philadelphia, enlivened the program with new songs and famous melodies.

Each year these Regional Meetings for Eastern Pennsylvania are growing in size and with enthusiasm among the members. Governor Bortz and a very active Governor's Committee deserve commendation and real recognition for the success of these meetings.

REGIONAL MEETING OF MONTANA MEMBERS OF THE COLLEGE

The Montana Branch of the American College of Physicians held their meeting at Billings, Mont., on February 15, 1941. The program began at 2:00 p.m. with case

reports and presentation of patients by Dr. Robert W. Currie (Associate) and Dr. Wayne Gordon, F.A.C.P., Billings, and by Dr. Meredith B. Hesdorffer (Associate), Missoula. Following the afternoon session the business session was held with dinner at 7:00 p.m. In the evening Dr. M. A. Shillington, F.A.C.P., Glendive, presented a study on "The Treatment of Hay Fever," followed by Dr. Charles F. Little (Associate), Great Falls, on "Chronic Obstruction of the Small Bowel." Fourteen members from over the state were present. Sessions were presided over by Dr. Ernest D. Hitchcock, F.A.C.P., College Governor for Montana.

Dr. O. H. Perry Pepper, F.A.C.P., Professor of Medicine at the University of Pennsylvania School of Medicine, Philadelphia, Pa., and Dr. Francis G. Blake, F.A.C.P., Professor of Medicine at Yale University School of Medicine, New Haven, Conn., have been appointed members of a four-man board to investigate, prevent, and control infectious diseases in the Nation's expanding armed forces by Secretary of War Henry L. Stimson.

The Tennessee State Medical Association has appointed the following Fellows of the American College of Physicians to its Committee on Postgraduate Instruction in Internal Medicine: Dr. J. Owsley Manier and Dr. Rudolph H. Kampmeier, Nashville, Dr. Franklin B. Bogart, Chattanooga, Dr. William C. Chaney, Memphis, and Dr. Robert B. Wood, Knoxville.

The 37th Annual Congress on Medical Education and Licensure was held in Chicago, Ill., February 17-18, 1941. Among the speakers at this meeting were:

Dr. C. Sidney Burwell, F.A.C.P., Dean, Harvard Medical School, Boston, Mass.—"A School of Dental Medicine";

Dr. Edward L. Turner, F.A.C.P., Meharry Medical College, Nashville, Tenn.—"Undergraduate and Graduate Medical Education for Negroes";

Dr. Reginald Fitz, F.A.C.P., Member, Council on Medical Education and Hospitals, American Medical Association, Boston, Mass.—"The Confused State of the Hospital Internship."

On March 13, 1941, Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., addressed a joint meeting of the Cape May County Medical and Bar Associations at Ocean City, N. J.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., has been appointed Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania. This is a newly formed committee and its projected plan will include the dissemination of the newer knowledge of nutrition—causes, prevention, early recognition and the medical management of nutritional deficiency.

Dr. Kelly was guest lecturer on the subject of "Calcium Metabolism and Its Abnormalities," before the Senior Class of the Woman's Medical College of Pennsylvania, January 24, 1941.

The New Jersey Gastroenterological Society will hold its Clinical Report Night and meeting at the Elizabeth General Hospital, Elizabeth, N. J., April 7, 1941. Among those who will participate in the program are: Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., Dr. Hyman I. Goldstein (Associate), Camden, N. J., Dr. Manfred Kraemer, F.A.C.P., Newark, N. J., and Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.

The National Gastroenterological Association will hold its 6th Annual Convention in New York, N. Y., May 13-16, 1941, under the presidency of Dr. Anthony Bassler, F.A.C.P., New York, N. Y.

Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., and Dr. Hyman I. Goldstein (Associate), Camden, N. J., are the delegates of the New Jersey Gastroenterological Society to the National Gastroenterological Association.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "Abdominal Pain" at a recent meeting of the San Francisco County Medical Society, San Francisco, Calif.

Dr. Robert T. Lucas, F.A.C.P., Shreveport, La., was recently elected Vice President from Louisiana of the Tri-State Medical Society of Texas, Louisiana and Arkansas.

Dr. Joseph O. Weilbaecher, Jr. (Associate), has been appointed Acting Director of Charity Hospital, New Orleans, La.

Dr. George Erick Bell, F.A.C.P., Wilson, N. C., has been elected one of the Vice Presidents of the Seaboard Medical Association.

Dr. James P. Rousseau, F.A.C.P., has been appointed Professor of Radiology at the new Bowman Gray School of Medicine of Wake Forest College in Winston-Salem, N. C.

Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn., has been elected Vice President, and Dr. Carl V. Moore (Associate), St. Louis, Mo., Secretary-Treasurer, of the Central Society for Clinical Research.

Recently Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Internal Medicine at the University of Michigan Medical School, Ann Arbor, delivered the Henry Sewall Memorial Lectures at the University of Colorado School of Medicine in Denver. He spoke on "The Therapeutic Value of Blood and Blood Substitutes" and "The Hemorrhagic Diseases."

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, spoke on "Treatment of Pernicious Anemia" at the annual clinic day, January 29, 1941, of the Mount Carmel Mercy Hospital at Detroit, Mich.

Commander John R. Poppen, F.A.C.P., (MC), U.S.N., Bureau of Aeronautics, was one of the lecturers at the 7th annual postgraduate course in ophthalmology and otolaryngology conducted recently at the University of Virginia Department of Medicine, Charlottesville, Va.

Among the guest speakers at the 56th annual session of the Mid-South Post Graduate Assembly held in Memphis, Tenn., February 11-14, 1941, were:

Major General James C. Magee, F.A.C.P., (MC), U.S.A., Washington, D. C.—"Medical Preparation for the Present Emergency";

Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.—"Digitalis, Its Indications and Best Method of Administration";

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—“Obesity, Types and Treatment.”

Dr. Charles H. Lutterloh, F.A.C.P., Hot Springs National Park, Ark., was named President-Elect of the society at this meeting.

Dr. Ernest L. MacQuiddy, F.A.C.P., Omaha, Nebr., has been named Associate Professor of Internal Medicine at the University of Nebraska College of Medicine, Omaha.

Dr. John H. Skavlem, F.A.C.P., and Dr. Leon Schiff, F.A.C.P., have been made Associate Professors of Medicine at the University of Cincinnati College of Medicine.

Dr. James B. Herrick, M.A.C.P., Chicago, Ill., delivered the Fifth Christian Fenger Lecture of the Institute of Medicine of Chicago and the Chicago Pathological Society on February 10, 1941. Dr. Herrick spoke on “Christian Fenger as I Knew Him, 1885-1902: A Study in Personality.”

Dr. Mark Gerstle, Jr., F.A.C.P., has been promoted to Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve and is on active duty as a neuro-psychiatrist at the U. S. Naval Training Station, San Diego, California.

Dr. Anthony Bassler, F.A.C.P., LL.D., presented a paper on “Recent Advances in Gastroenterology” at a meeting of the Philadelphia chapter of the National Gastroenterologic Association, January 16, 1941. Before the Mid-Hudson chapter of the Montclair Medical Society, February 15, he read “The Intestine and Chronic Arthritis.” “Pathologic and Clinical Aspects of Gall-Bladder Disease” was presented at the Academy of Medicine at Buffalo, February 26. He gave an address over WABC on the subject of “Dieting for Indigestion” for the New York Academy of Medicine, February 1.

OBITUARY

DR. FRANCIS EDWARD STEWART

Dr. Francis Edward Stewart, F.A.C.P., born in 1853, died February 21, 1941 at his home in Greene Manor Apartments, Greene and Johnson Streets, Germantown, Philadelphia, after a two months' illness. He is survived by two daughters, Mrs. Gilbert M. Tucker, Albany, and Miss Marjorie Mathews Stewart.

Dr. Stewart was a Graduate in Pharmacy from the Philadelphia College of Pharmacy in 1876, from where he also obtained his Master in Pharmacy. He became a Doctor of Medicine from Jefferson Medical College in 1879.

Some of the honors and degrees which Dr. Stewart enjoyed were: Fellow of the American Medical Association; Fellow of the American College of Physicians; Fellow of the American Academy of Medicine, June 9, 1916; Fellow of the American Therapeutic Society, being also one of its founders in 1900, and Chairman of its Committee on Organization. He was a life member and Honorary President of the American Pharmaceutical Association and Chairman of its Committee on Patents and Trademarks. Honorary life member of the American Medical Editors and Authors Association; honorary life member of the Pennsylvania Pharmaceutical Association.

Dr. Stewart also claimed distinction as a teacher, being associated with such renowned colleges as the Medico-Chirurgical College of Philadelphia, where he was Professor of Materia Medica, Botany and Physiology; Jefferson Medical College, where he was a Demonstrator and Lecturer on Materia Medica and Pharmacy; Women's Medical College of Pennsylvania and the Philadelphia College of Pharmacy where he was quiz master in Pharmacy and Chemistry.

In addition to the tasks already imposed upon him by the preceding facts, Dr. Stewart was also Associate Editor of the *Therapeutic Gazette* (1882). He was instrumental in selecting Professor Horatio C. Wood and Robert Mead Smith as editors in 1884-5 and transferring the editorial and publication headquarters to Philadelphia. He was associate editor also of the *Medical Bulletin*. Dr. Stewart was founder and director of the Scientific Department of Parke, Davis and Co., and his contributions to Frederick Stearns and Co., and the H. K. Mulford Co. are well known. His book "Stewart's Compend of Pharmacy" holds a place of esteem in the Pharmaceutical literary field.

Dr. Stewart has been a Fellow in the American College of Physicians since 1918 and never has his loyalty and interest waned. His death ends the career of a brilliant and gentlemanly scholar.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

BOSTON SYMPHONY CONCERT FOR MEMBERS AND FRIENDS OF THE COLLEGE DURING BOSTON SESSION

(TUESDAY EVENING, APRIL 22, 1941)

Dr. Serge Koussevitzky, Conductor of the Boston Symphony Orchestra, has invited members and friends of the College to a concert at Symphony Hall, Massachusetts and Huntington Avenues, on Tuesday evening, April 22, during the Twenty-Fifth Annual Session of the College in Boston. Guests are requested to come at 8:45, in ample time before the doors close at 9:00 p.m. Tickets will be distributed free at the Hotel Statler on Monday and Tuesday, April 21 and 22. An opportunity to reserve seats ahead of time is also afforded to members who shall communicate with the Executive Secretary of the College.

The Boston Symphony Orchestra is noted for its superb performances, its pre-eminence, the vision and pertinacity of its leader, and its remarkable personnel. Henry L. Higginson assembled sixty players under the present name more than sixty years ago. Mr. Higginson's dreams were unique mainly in the strength of conviction which lay behind them, and the ability to produce tangible results. It was the response they aroused in fellow New Englanders which made the growth of the Boston Symphony Orchestra possible. It is said that Boston citizens of 1881 waited all night in a queue for their first season tickets, which showed a trait traceable to the earlier New England which strove for music while it was yet eclipsed by the literary arts. The trait can be described as the determination to experience beauty at its highest. It persists in the audiences of today who treasure their weekly concerts as their main source of musical renewal and growth.

George Henschel, from England, was the first conductor, serving until 1884. The second conductor was Wilhelm Gericke who served from 1884 to 1889, succeeded by Arthur Nikisch from 1889 to 1893. Mr. Gericke returned in 1898, serving until 1906, being succeeded by Karl Muck who conducted the Orchestra from 1906 to 1908 and from 1912 to 1918. In the spring of 1918, Mr. Higginson, the founder, who had now passed his eightieth year, was ready to relinquish what had become through external circumstances a heavy burden. He had given America an illustrious example of what symphonic performance could be. That accomplishment, the act of one man carried through thirty-seven years, has had no counterpart.

Judge Frederick P. Cabot, president of a board of trustees, assumed responsibility for the orchestra. In response to appeals from Judge Cabot and his associates, a relatively small number began, and individuals since that time have continued, to contribute towards its maintenance. The organization of the society of the Friends of the Orchestra has placed that charge in the hands of a large and growing portion of those who attend the concerts and consider them indispensable.

Serge Koussevitzky, the present conductor, before coming to Boston, had organized and conducted an orchestra in Moscow and St. Petersburg. He was accounted a leader of commanding power, a pioneer ready to break a lance for new music by publication and by performance. He conducted in western Europe, and his *Concerts Koussevitzky* in Paris were found a new and electrifying experience. When Dr. Koussevitzky assumed leadership of the Boston Symphony Orchestra in 1924, it was immediately evident that the future of the orchestra was in the hands of a leader of extraordinary courage and brilliance, a musician of sensitive sympathy and emotional penetration. The orchestra passed the half-century milestone with Koussevitzky at its head—more than one quarter of its years under his leadership. They have been years of a single and uninterrupted leadership, of stability in membership and of the coördination which these conditions have made possible. The present expansion of

the orchestra's activities is the result of these years. Extra-seasonal activities, including the foundation of a unique school, now leave only the month of September without concerts.

The orchestra's public and its influence in behalf of music have vastly grown. This has been accomplished without compromise. A great artist in the fullness of his day, Koussevitzky's art is always an adventure, a new testing.

It is the hope of the College that its members and friends at the Boston Session will take advantage of this unusual opportunity for an evening of fine music, and that their appreciation will be duly shown by an attendance filling Symphony Hall.

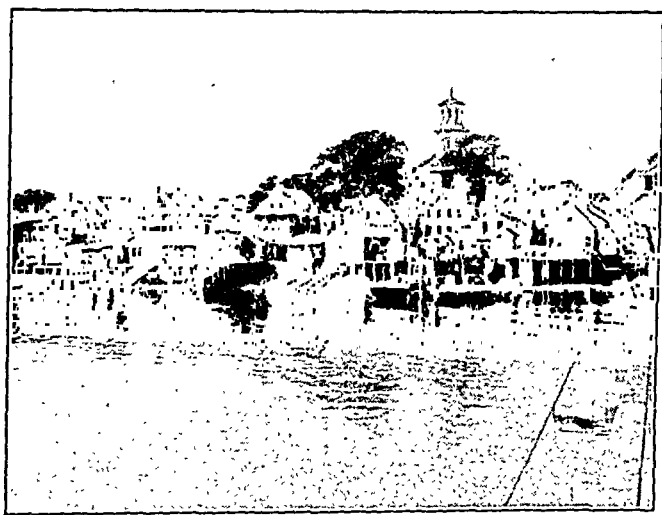
POST CONVENTION TOUR TO PLYMOUTH, THE PILGRIM SHORE, AND CAPE COD

(A continuation of the article from the February, 1941 issue of this journal)

For members and friends of the American College of Physicians, a post convention tour to Plymouth, the Pilgrim shore, and Cape Cod, has been arranged under the personal guidance of Mr. Leon V. Arnold, 36 Washington Square, West, New York City. The party will leave the Hotel Statler at 5:30 p.m., Friday, April 25, by de luxe motor coaches, visiting Plymouth, Sandwich, Barnstable, Yarmouth, Dennis, Brewster, Orleans, Provincetown, and other points of interest on Cape Cod, returning to Boston on Sunday, April 27.

The pulse always beats a little faster at the mention of Plymouth and the Pilgrim Shore. No places in America have greater historic and romantic appeal than Plymouth and her sister settlement, Jamestown. But because of the rigors of the climate, the hardships endured, and the results of the settlement there is probably the more sentiment about this early colony.

Cape Cod is quaint, precise. There is a dignity and primness in its villages. Its entire atmosphere takes you into the past by centuries and that is a long time before the Victorian era. The trip in Plymouth and along the North Shore of Cape Cod was described in the February issue of this Journal.



Provincetown.

After lunch we leave old Provincetown with its narrow winding streets, its picket fences and red chimneys, its gray gables and tiny gardens, its sand dunes and Town Hill surmounted by the granite shaft of Pilgrim Tower by the King's Highway. We return by the South Shore of the Cape which has a completely different aspect and character than the North. Less interesting? No, emphatically no.

At the very elbow of the Cape, sometimes called the funny bone, lies Chatham. You *must* pronounce both H's. Here William Nickerson of Yarmouth purchased a thousand acres of land from the Indian Sachem of the region by the down payment of a boat and in 1664 moved his family. Such a "concentration of wealth" placed him in difficulty with the General Court, but before he died he increased his holdings to

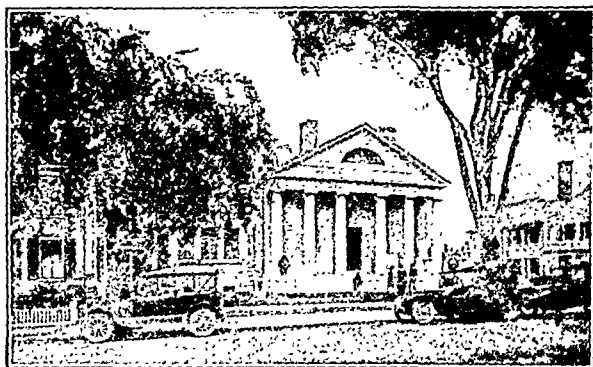
four thousand acres. Today Chatham is sophisticated but fascinating, a fashionable resort and very popular with the summer set. Here is the home of Joseph C. Lincoln whose books you have so much enjoyed.

As we swing west we get long glimpses of marine views. Many of the South Shore villages that we pass through were children of the earlier settlements of the North Shore to which today have been added the beautiful homes of the summer colonists.

Harwich was incorporated in 1694. It was the home of Captain Jonathan Walker, hero of Whittier's poem, "The Branded Hand." Today Harwich is the center of a great cranberry industry.

Along this shore sailed Gosnold in 1602 with his company of gentlemen adventurers. They made landings at various places with the intention of making a settlement, but there was dissension among them regarding a division of the spoils as well as trouble with the Indians and they loaded the ship with cedar, firs, and sassafras and returned to England. Later they returned to Jamestown.

Hyannis is the largest town of the Cape, its metropolis, and on all sides are estates and superbly located homes.



Pilgrim Hall, Plymouth.

Falmouth is another old town and a rich one, once the home of many deep-water sea captains whose stately homes still stand. Just across the sound lies Martha's Vineyard, one of New England's most loved resorts and as quaint a bit of land as one would expect to find a thousand miles distant.

From Falmouth we turn another corner and follow the shore of Buzzard's Bay, a beautifully broken coast line of little inlets and rocky, wooded capes. The first settlers were farmers and fishermen. The later settlers seek health and recreation. Among the most famous of these have been Joseph Jefferson and Grover Cleveland. Both lived on these shores and fished the Bay together.

At Bourne we cross the Canal and leave the Cape. Cape Cod begins at the Canal. Governor Bradford and Miles Standish knew this country well and in 1756 ninety Acadians who were exiles from their homes settled here.

Soon after leaving Plymouth on the morning of the 27th we stop in Duxbury to visit the Miles Standish Monument and the home of John Alden and Priscilla. En-route we see Marshfield, the home and tomb of Daniel Webster, the House of Old Oaken Bucket fame, the Old Ship Meeting House, 1681, said to be the oldest church in the United States. We follow the Ocean Shore Drive and Jerusalem Road and pass through Hingham, settled in 1635, and still retaining some of its colonial charm. In Quincy we visit the Adams Mansion, 1634, the home of John Adams and John Quincy Adams and reach Boston for the early afternoon train departures, completing our brief tour of "the Nation's Birthplace."

The price quoted, \$27.75, includes absolutely every necessary expense. Even Webster would approve of the use of the term "absolutely," for you do not need to spend one nickel, not even for a tip, from Boston back to Boston.

If you have not already sent in your reservation, do it *NOW*. The accommodation remaining is limited. If you must change your plans later, your deposit will be refunded. This is a real opportunity that should not be passed up lightly.

Send your deposit or ask any questions that you may wish regarding the trip to Leon V. Arnold, 36 Washington Square West, New York City. Mr. Arnold will accompany the party.

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SOME ASPECTS OF THE NATURE OF THE CHEMICAL CHANGES OCCURRING IN ATHEROMATOSIS*

By IRVINE H. PAGE, *Indianapolis, Indiana*

VIRCHOW was the first to recognize that atheromatosis might result from loosening of the connective tissue ground-substance, of which the arterial intima is for the most part composed, and subsequent infiltration with fat from the blood stream. The loosening of the ground-substance was believed to be caused by mechanical strain. Aschoff and Ribbert in particular have championed this so-called "infiltration theory."

Aschoff¹ thought that the fatty material deposited in vessels consisted almost exclusively of cholesterol esters coming from blood plasma which nourished the vessel wall. He agreed with Virchow that those regions of the vessels which are under greatest mechanical strain, such as the mouths of the intercostal vessels, are especially apt to exhibit atheromatosis. But he² postulated a second factor which he believed *must* be present before atheromatosis appears, viz., a sufficient concentration of lipids, especially cholesterol esters, in the plasma. "From plasma of low cholesterol content no deposition of lipoids will occur, even though mechanical conditions are favorable. The greater the concentration of the cholesterol esters in the plasma, the more surely will the areas of the aorta subject to the greater mechanical strain show this fatty deposition even macroscopically." His view that the concentration of lipid may be greatly altered by the amount ingested in the diet was used to account for the observed decrease in atheromatosis in the later years of the war and in the post-war period in Germany.

Aschoff's theory is summed up in his own words: "As we consider the atheromatosis of the vessels in the light of the larger category of the general processes of wear and tear of the supporting substances, it loses its special qualities, which have given rise to so many erroneous theories of infection, etc. If that process of wear and tear impresses us most strikingly in the

* Lecture presented before the Philadelphia Metabolic Association December 8, 1934.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital Indianapolis, Indiana.

vessel wall, it is due to the fact that our vascular system is the organ which is mechanically under greatest strain."

Let us now consider in more detail several of the important postulates in the "infiltration theory" of atherosclerosis starting with more general questions of lipid metabolism.

1. *Is the level of lipid in the blood controlled by the amount of lipid in the diet?* Bloor³ found that the plasma of normal dogs fed over long periods of time with high fat diets contained somewhat more lipid than dogs under similar conditions but on diets low in fat. Rabbits exhibit this phenomenon more strikingly than dogs. Bloor explained this on the basis of the fact that dogs are racially accustomed to fat while rabbits are not.

Corwin⁴ showed that diets high in fat may or may not produce moderate hypercholesterolemia in dogs. Lecithin from adrenal glands, when given by mouth daily, constantly raised the concentration of cholesterol in the blood. When lecithin is added to the high fat diet, marked elevation of blood cholesterol occurs. These experiments were extended by Flock, Corwin and Bollman⁵ demonstrating that sustained post-absorptive hyperlipemia occurs when dogs are fed phosphatide, even when the fat content of the diet is not greater than 8 per cent. Feeding increased amounts of neutral fat or cholesterol did not greatly alter the blood lipids.

Similar controlled experiments in normal man do not appear to have been carried out. It may be noted, however, that the Eskimo of the Canadian Eastern Arctic, whose diet normally consists largely of protein and fat, show no increase in any of the plasma lipid constituents (Corcoran and Rabino-witch⁶²). The level of blood cholesterol is little affected in the white man (Tolstoi⁶³) by long-continued administration of similar diets.

Hyperlipemia occurs commonly in severe, uncontrolled diabetes mellitus (Allen⁶). Opinions differ as to the effects of dietary fat in this condition. Some investigators believe that high fat diets do not contribute to the maintenance of hyperlipemia,⁶ some suggest the contrary¹¹ and still others have found that hyperlipemia may be reduced while feeding diets high in fat.^{7, 8} Wishart⁹ found no decisive influence on lipemia of diets high or low respectively in cholesterol or lecithin. Experimental diabetes due to partial pancreatectomy in dogs, uncontrolled by insulin, results in lipemia when either low or high fat diets are fed. Contrariwise, total pancreatectomy in dogs maintained with insulin results in marked lipopenia, with disappearance of cholesterol ester from the blood and accumulation of lipid, other than phosphatides, in the liver (Kaplan and Chaikoff⁶⁴). Addition of raw pancreas to the diet not only decreased the lipid content of the liver, but also effected a rise of blood lipids to values far in excess of normal or preoperative levels.⁶⁶

Administration of insulin alone to diabetics in ketosis may, within a few hours, result in a reduction of lipemia, due largely to decreases in plasma triglyceride and phosphatide, while cholesterol is little affected (Corcoran

and Rabinowitch⁶⁵). Subsequent administration of high-carbohydrate, low-fat diets to these patients failed to result in further reductions of plasma lipids. Rabinowitch¹¹ believes that the administration of such diets delays the development of atherosclerosis in diabetics and presents strong statistical evidence in support of this view. It is probable that the sustained reductions of plasma cholesterol in diabetics on low-caloric, high-carbohydrate, low-fat diets are due to improved control of the diabetes by these diets, rather than to the fat content of the diet as such.

There were no data in the literature on the effect of variations of the fat content of diets on plasma lipids of patients suffering from nephrosis, and consequently Dr. Farr and I¹⁰ studied a group of such patients. The experiments lasted several months and the fat was varied from 8 to 65 per cent of the total calories. Protein was kept constant and carbohydrate added in sufficient amounts to keep total calories unchanged. We found no regular influence of these wide shifts in the fat content of the diet on the plasma lipids. It was concluded, therefore, that fat may be included in the diet of patients with nephrosis and hyperlipemia without fear of further elevating the blood lipids.

To sum up, it appears that fat, like sugar, normally increases in the blood shortly after administration of a fat meal, although this increase may be less marked in those accustomed to the ingestion of large amounts of fat (Corcoran and Rabinowitch⁶²), but that the post-absorptive level in the Eskimo, in nephrotic patients, and in diabetics metabolising adequate amounts of carbohydrate, is not appreciably affected by high-fat diets. Fat absorbed from the alimentary canal is quickly deposited in tissue depots prior to utilization and during post-absorption periods of fasts the concentration of circulating plasma fat is maintained by mobilization from these depots (Schönheimer and Rittenberg¹²). This conception is clearly at variance with the belief that lipemia and perhaps atherosclerosis may be avoided or at least not aggravated by interdicting ordinary amounts of fat-containing foods. In the light of the evidence cited, one does not appear justified in depriving patients of diets containing an ordinary proportion of fat. Definite harm may result from a fat-free diet because of the difficulty of maintaining an optimum state of nutrition, and such a diet should not be given unless a definite therapeutic advantage can be demonstrated for it. That advantage does not appear to exist.

2. *Is hyperlipemia necessary for the development of atherosclerosis?* If hyperlipemia were necessary for development of atherosclerosis, then increased amounts of lipid should be found in the plasma of patients during its development. The available data in the literature showed no agreement on whether unusual fat and cholesterol concentrations exist in the serum of patients with hypertension in whom atherosclerosis is so prevalent. Nor do the data agree in showing whether the serum is supersaturated with free cholesterol. Page, Kirk and Van Slyke¹³ studied the first problem. The

gasometric method of Kirk, Page, and Van Slyke¹⁴ for the determination of plasma lipids was employed. In 16 patients with uncomplicated essential hypertension the concentration of total lipids or any of the lipid fractions which included free and esterified cholesterol, lipid amino nitrogen, total lipid nitrogen and lipid phosphorus were normal. The means and standard deviations of the group were not significantly different from those found in a group of normal subjects. It was concluded that theories of the genesis of atheromatosis in essential hypertension based on presumed hyperlipemia or hypercholesterolemia, or on elevation of the cholesterol: phosphatide ratio are without basis. Evidently atherosclerosis can develop in the absence of hyperlipemia.

Alvarez and Neuschlosz¹⁵ found that serum from patients with hypertension was supersaturated with cholesterol. They ascertained this by adding free cholesterol to the serum and determining the amount dissolved. If it were true that serum of these patients is supersaturated with cholesterol, even though the level of it in the serum be normal, precipitation in tissues might occur more readily than if it were not saturated. Holden¹⁶ and Medvei¹⁷ were unable to confirm this work. The serum of both normal subjects and patients with hypertension were approximately saturated with cholesterol. It is concluded that no abnormality in the blood has yet been found in patients with essential hypertension which accounts for the precipitation of lipids into the vessel walls with development of atherosclerosis.

Landé and Sperry¹⁸ were unable to find any relation between the cholesterol content of serum and the degree of atherosclerosis present in 123 supposedly healthy persons who died suddenly from violence.

From these results it appears that hyperlipemia is not essential for development of atherosclerosis.

3. *May hyperlipemia favor development of atherosclerosis?* The increased incidence of atherosclerosis in cases of diabetes, nephrosis, xanthomatosis, and Hand-Schüller-Christian syndrome has suggested to many clinicians that hyperlipemia strongly aids in the development of atherosclerosis.

Gibbs, Buckner and Bloor¹⁹ showed that the group of diabetics with the most advanced sclerosis showed the highest total and esterified plasma cholesterol content, and that the proportion of cholesterol in esterified form was 10 to 15 per cent above the usual normal values. White²⁰ found that diabetics with high plasma cholesterol values were 15 times as likely to develop atherosclerosis as diabetics with normal cholesterol. Rabinowitch²¹ also found close association between hypercholesterolemia and atherosclerosis in diabetic patients.

The presumptive clinical evidence that hyperlipemia favors atherosclerosis is supported by the experimental investigation of Anitschkow,²¹ who demonstrated that rabbits fed large quantities of cholesterol develop lesions in their arteries similar in many respects to human atherosclerosis. The work of Anitschkow and recently that of Leary²² appears to show that the resem-

blance is more than superficial. The clinical observation that hyperlipemia and atherosclerosis are often associated, and the experimental production of atherosclerosis by hyperlipemia in rabbits support the belief that hyperlipemia aids in the process of atheroma formation.

Whether hyperlipemia alone can produce atherosclerosis in man is not known. Even in patients suffering from nephrosis with hyperlipemia, where other factors than hyperlipemia may prevail, atherosclerosis may not be present. It is possible that this is due to the fact that the hyperlipemia is not long enough sustained, but again other factors may be involved of which we are ignorant.

Although feeding cholesterol to rabbits produces atherosclerosis in them with ease, the same procedure does not produce it in omnivora, such as rats, cats and dogs. This has been explained as due to inability of rabbits to metabolize properly a substance which is foreign to their diet. Herbivora normally consume diets rich in vegetable sterols, the so-called phytosterols. These substances such as ergosterol, zymosterol and sitosterol though resembling cholesterol in structure are not isomeric with it. They are absorbed from the gastrointestinal tract but only in small amounts (Menschick and Page,²³ Schönheimer and Dam²⁴). The most convincing demonstration of this was the demonstration that hens fed ergosterol laid eggs containing amounts of ergosterol greater than normal.

It appears somewhat improbable that cholesterol in the rabbit's body is derived from the phytosterols contained in its diet. We assume that rabbits synthesize most or all of their cholesterol, in marked contrast with omnivora which derive relatively large amounts of it from their food. It is possible that cholesterol added in large amounts to the diet of animals ordinarily accustomed to synthesizing their entire supply greatly overloads the usual regulatory mechanism.

But how does this "overloading" find expression in these animals? Yuasa²⁵ pointed out that there was a qualitative difference in distribution of cholesterol in cats and rabbits fed it. The livers of cats become enlarged and the cholesterol content rises. The remainder of the organs show but slight increase in their sterol content. Contrast this with the distribution in rabbits fed cholesterol. The liver is slightly increased in size and the sterol content increased very moderately. The remainder of the organs, however, show increase in sterol, well above the corresponding figures for cats. Menschick and Page²⁶ investigated this problem quantitatively and found the following results for the two groups of animals:

Liver—rabbit—increase in sterol content 4–9 times

Liver—cat—increase in sterol content 30–40 times

Remainder of organs—rabbit—increase in sterol content 1–4 times

Remainder of organs—cat—increase in sterol content 1–1.4 times.

Clearly the distribution of cholesterol is diffuse in rabbits, while in cats cholesterol is concentrated in the liver. The liver of rabbits appears unable

to withhold cholesterol from general circulation. It is, therefore, possible that the reason atherosclerosis may be produced in rabbits with ease, and not at all in omnivora, is that rabbits allow cholesterol to circulate freely, continuously subjecting the arteries to plasma containing more than normal amounts of it, while cats prevent this by depositing the sterol in the liver. While this seemed to us a plausible explanation of the discrepancy between the response of herbivora and omnivora, it may be only a special case and have little to do with the development of atherosclerosis in man. Future investigation must decide whether relative incompetence of the liver to accumulate cholesterol exists in certain human beings as it does in rabbits.

In summary, it appears that at least two factors can assist in producing human atherosclerosis. One of these is lipemia, and it appears to be important in diabetes, nephrosis and xanthoma. The other factor or factors act in the cells of the arteries themselves. Presumably it is some change that may be started by the strain of prolonged hypertension. In hypertension these factors alone, without hyperlipemia, suffice to produce atherosclerosis.

4. *Can the difference between herbivora and omnivora with regard to their susceptibility to cholesterol atherosclerosis be due to differences in their ability to destroy cholesterol?* Since the experiments of Gamble and Blackfan²⁷ and Channon²⁸ there is little doubt that both herbivora and omnivora can synthesize cholesterol.

TABLE I
Destruction of Cholesterol

	Adminis- tered Cholesterol	Excess Excretion	Deposited in Animal	Total Sterol Found	Cholesterol Destroyed in Grams	Per Week	Length of Experiment Weeks
Rabbit	37.9	13.6	0.6	14.2	23.8	1.8	13
	15.4	4.8	4.2	9.0	6.5	1.6	4
	19.3	7.9	5.9	13.8	5.4	1.1	5
	18.9	7.3	3.2	10.5	8.3	1.2	7
	24.3	13.9	3.0	16.9	7.4	0.8	9
Cat	22.5	10.4	6.4	16.8	5.7	1.5	days 26
	21.2	10.0	5.2	15.2	6.0	2.1	20
	20.2	8.8	6.4	15.2	5.0	1.7	20

Proof that degradation occurs was afforded by experiments that Menschick and Page²⁹ carried out in 1931. Rabbits were fed relatively large amounts of cholesterol and the intake and output of sterol measured. At the end of the experiment the animals were killed and the carcass analyzed. It was shown that from 0.8 to 1.8 grams of cholesterol was destroyed in a week over experimental periods of months. Cats also possessed this power. Subsequently Schoenheimer and Breusch³⁰ found that mice either synthesized or destroyed cholesterol according to the amount fed them.

If it could be shown that omnivora destroy cholesterol at a much greater rate than herbivora, this might explain the fact that production of athero-

sclerosis by cholesterol feeding is impossible in omnivora, but easy in rabbits. Balance experiments were consequently performed on cats to compare with the data on rabbits. To our surprise, destruction was at about the same rate as in rabbits. We were forced to conclude that difference in rate of degradation of cholesterol was not the cause of the species difference in susceptibility to experimental production of cholesterol atherosclerosis.

5. *Is old age associated with hyperlipemia?* If hyperlipemia developed simultaneously with increase in age it would be not unreasonable to suppose that it would predispose to development of atherosclerosis. Indeed this supposition has appeared in the literature. However, study of the plasma lipids in old age shows not the slightest tendency for lipemia to develop. Five years ago, in association with Kirk, Lewis, Thompson and Van Slyke,³¹ the opportunity was afforded to reexamine this question. The subjects were men who by most careful clinical examination were healthy. They were on unrestricted diets. The post-absorptive lipids were examined by the gasometric method of Kirk, Page and Van Slyke.¹⁴ It was found that variation of age from 20 to 90 years had no determinable influence on either the amount or the composition of the plasma lipids. It follows that old age does not cause hyperlipemia.

6. *Does increase in mechanical strain on arteries aid in development of atherosclerosis?* Pathologists have, I believe, answered this question in the affirmative in a satisfactory manner. Casual inspection of arteries at autopsy will readily convince one that the points in the vessels subject to the greatest mechanical strain are those earliest and most severely involved. In young persons with congenital constriction of the aorta, atheroma usually occurs proximal to the constriction and not distal to it. Aortic narrowing may cause hypertension in the portion proximal to the stenosis. Oberndorfer³² especially has pointed out that movement and massage of vessels is likely to better their nutrition and prevent sclerosis. Arteries which are fixed to bony structures show the most marked sclerotic changes. For example, the posterior wall of the aorta is usually more involved than the anterior, the femoral artery more than the popliteal. Besides freedom from fixation and local increase in pressure the arteries appear to be more subject to atherosclerosis when the systemic arterial pressure is elevated. There is no complete proof that increased pressure alone can cause atherosclerosis, but as yet in patients with essential hypertension no other factor is known. At least the factor of hyperlipemia is not operative here. Moon³³ has made an important suggestion which may offer at least a partial explanation for the occurrence of atheromatosis in hypertension. He has shown, by applying hydrodynamic principles, that at certain points in arteries where the arterial pressure is highest, local tissue anemia may result from compression of the nutrient capillaries in the arteries. As Moon states, "The occurrence of degeneration at the bifurcation of the aorta and in narrow zones immediately surrounding the orifices of arteries leaving the aorta is characteristic of the

earliest atheromatous degeneration. These are areas in which minimal degrees of hypertension would exert maximal pressure effects, because in these areas such pressure would be exerted on the wall from two directions. Hence slight hypertension might cause local anemia of the artery wall earlier than in areas in which the pressure would be exerted in only one direction."

7. *Are there factors other than increased pressure and hyperlipemia which aid in production of atherosclerosis?* To answer this problem we must turn back to the experimental production of atherosclerosis in rabbits. Feeding cholesterol in oil to these animals results in marked atherosclerotic changes as Anitschkow showed. An observation of great interest was made 8 years later by Murata and Kataoka.³⁴ They found that simultaneous administration of thyroid along with the cholesterol prevented deposition of lipids in the aorta. Their brief publication was not followed by a detailed communication and the observation appears to have been forgotten. Liebig³⁵ took it up 12 years later and convinced himself of the correctness of the experiments. Turner has added further important observations. He showed that potassium iodide as well as thyroid exerted protective action, and, with Khayat,³⁶ that when the thyroid gland is removed from the animal, potassium iodide no longer exerts this action. Their results showed that potassium iodide prevented the usual hypercholesterolemia and that there was a relationship between the development of atherosclerosis and hypercholesterolemia. If it could be proved that administration of thyroid prevented development of atherosclerosis by preventing hypercholesterolemia, it would offer strong support for a unitary conception of the development of atherosclerosis in cholesterol-fed rabbits. But it seemed to Bernhard and Page³⁷ that this view failed to offer any clue as to why the deposition of lipid is so sharply localized, nor was it known whether thyroid prevented deposition of other lipids than cholesterol. If hyperlipemia were the only factor, atherosclerosis should be generalized. Consequently, we undertook to study the problem again using gasometric methods for our lipid analyses.

Instead of potassium iodide we employed an organic preparation of iodine, the di-iodide of ricinsterolic acid. According to Wottschall³⁸ this preparation does not irritate the stomach and the iodine remains in the blood stream longer than other preparations of iodine tested. Somewhat to our surprise we found that instead of lowering the various lipids in the blood it raised them above the level in the plasma of control animals fed approximately the same amounts of cholesterol in oil. Yet formation of atherosclerosis was largely prevented in the iodide-fed animals. It appeared that animals fed iodine and cholesterol developed greater hyperlipemia, yet in spite of this, the lipids did not deposit in the arterial walls. It was concluded that some other important factor as well as hyperlipemia played a part in the production of experimental atherosclerosis. What this third factor is that appears to influence the receptivity of tissues to the deposition of lipids is unknown.

Iodine is not unique in its ability to prevent deposition of lipids. Large doses of potassium thiocyanate are effective.³⁹ Colloidal silicic acid,⁴⁰ garlic oil,⁴¹ and lipocaic⁴² are also believed to be active. Choline is either ineffective⁴³ or delays deposition.⁴⁴ Eberhard⁴⁵ made the interesting observation that the cholesterol content of the blood rose more rapidly and to higher levels in animals receiving both cholesterol and alcohol but deposition in the liver and aorta was considerably less in the animals receiving alcohol as well as cholesterol.

It appears that in favoring production of atherosclerosis, there is in addition to lipemia and hypertension, a third factor. This factor is characterized at present only by the fact that it is neutralized in the rabbit by iodine and thiocyanate administration and probably a number of other substances.

8. *Does the lipid mixture deposited in the arterial wall resemble that in plasma?* Let us now consider the composition of the lipid material deposited in the vessel walls. Aschoff⁴⁶ especially has emphasized the high cholesterol content and this was confirmed by chemical analysis by Windaus⁴⁷ and Schönheimer.⁴⁸ It was not shown whether the atheromatous deposits contained lipid mixtures similar to the plasma lipid mixture, or whether the atheromatous deposits exhibited a different and characteristic lipid composition, though important work suggested it.^{49, 50, 51} The following table presents the results of our analyses. For comparison the average composi-

TABLE II
Comparison of Data of Lipid Analysis of Advanced Atherosclerosis

Total Lipid	Total Cholesterol	Grams of Lipid in 100 Grams of Moist Tissue					Tissue	Author
		Free Cholesterol	Ester Cholesterol	Phosphatide	Total Lipid Nitrogen	Lipid Amino Nitrogen		
9.4	4.8	—	—	1.7	—	—	non-diabetic	Lehnherr
13.4	7.8	—	—	2.4	—	—	diabetic	Lehnherr
8.4	4.3	2.1	2.1	1.4	—	—	non-diabetic	Meeker and Jobling
—	4.8	3.0	1.7	1.8	—	—	non-diabetic	Zeek
12.5	7.2	2.4	4.9	1.9	0.18	0.138	non-diabetic	Page

TABLE III
Composition of the Lipid Mixture from Atherosclerotic Aortas

Total Cholesterol		Percentage of Total Lipids as				Atomic Ratios		Author
		Free Cholesterol	Ester Cholesterol	Phosphatide	"Neutral Fat"	Total N Lipid P	Amino N Lipid P	
Lipemic plasma	47.6	—	—	18.3	—	—	—	Lehnherr
	53.7	—	—	17.9	—	—	—	Lehnherr
	51.0	25.4	25.5	16.9	—	—	—	Meeker and Jobling
	57.0	18.0	39.0	14.0	33.0	4.9	2.8	Page
	48.0	12.0	36.0	22.0	30.0	3.0	0.99	Page, Kirk and Van Slyke

tion of lipemic plasmas is introduced. Comparison shows that the lipid mixture deposited in the vessel wall resembles to a marked degree the lipid mixture of the plasma.

It appears from preliminary analyses that the same is true in rabbits with experimental atherosclerosis. As yet we have had opportunity to analyze but two such aortas. Surprisingly the lipids in the aortic lesion exhibited about the same composition as in lipemic rabbit plasma. It might be supposed that feeding cholesterol in oil would not produce hyperlipemia characterized by increase in all of the lipids which are at present measurable, such as lipid amino nitrogen, total lipid nitrogen, etc., but actually this is true. All of these constituents rise very nearly proportionally. Lipids other than cholesterol and its esters are involved in the formation of experimental atherosclerosis in rabbits fed cholesterol just as in the spontaneous human disease.

Atherosclerosis either in human beings or in rabbits is thus not a disorder in which cholesterol alone is involved. The other lipids are also concerned and almost in the proportion that they exist in the lipid mixture of plasma.

9. *Is there evidence that chemical change of the lipids deposited in vessel walls occurs?* Klotz⁵² in 1905 put forward an attractive theory to explain the origin of calcification in lipid plaques in aortas. He held that esters of cholesterol after deposition were split, free cholesterol crystallized out, and the free fatty acids combined with calcium to form insoluble calcium soaps. The evidence on which this was based was derived largely from staining reactions. Wells⁵³ soon showed by chemical analysis that the deposited calcium resembled bone rather than calcium soaps in composition. Baldauf⁵⁴ also showed that no calcium soap was present in atheromatous aortas. Schönheimer⁴⁸ confirmed Wells' observations and further demonstrated that cholesterol esters increased rather than decreased with increase in severity of the lesions. This observation precluded splitting of cholesterol esters. Recently, however, this result has been elaborated by both Meeker and Jobling⁴⁹ and Zeek.⁵¹ They find that the ratio of free to ester cholesterol decreases during the early stage of the atheromatous process but shows a marked increase in the advanced lesions. Evidently further work is necessary to clarify this point, with more attention given to the extent and severity of the lesions.

Menschick and I⁵⁵ became interested in this problem from another point of view. We wished to know whether in such lipid deposits, which are morbid in character, decomposition products of cholesterol could be found. We had searched for them in vain among the sterols present in normal brain by means of the ultraviolet spectrograph. But in the sterols from atheromatous lesions a band was found in the spectrogram with absorption maxima at 238 m μ and 320 m μ . Repeated fractionation with alcohol enriched the substance in solution and the band remained unaltered. The spectrogram

was practically identical with that described by Heilbron, Morton and Sexton⁵⁶ for cholestenone, the ketone of allocholesterol. It was concluded that this substance represented a stage in the degradation of cholesterol in the body. That it is not exclusively associated with the atheromatous process is shown by the fact that much smaller quantities of the substance could be separated from normal aortas.

It cannot be taken that the finding of cholestenone means active degradation of sterols in the aorta. It *may* mean that this is occurring but the observation could equally well be explained on the basis of selective absorption of it from the blood stream. Whatever the explanation, it is interesting that study of atheromatous lesions led to the separation of a degradation product of cholesterol. Others have, so far, not been found. The evidence on which the belief is based that cholestenone represents a stage in the metabolism of cholesterol has lately been strengthened by Schönheimer, Rittenberg and Graff's⁵⁷ demonstration that cholestenone when fed to dogs may be converted into either cholesterol or coprosterol.

The evidence, then, is insufficient to decide whether chemical metamorphosis occurs in atheromatosis. Most of the data suggest that it does not occur to a large extent except in the phosphatide fraction. The severity of the lesion and the occurrence of necrosis may determine the extent of the chemical alteration.

10. *How can the known factors which predispose to atherosclerosis be controlled?* This problem resolves itself in our present state of knowledge to consideration of three factors: First, prevention of hyperlipemia, second, prevention of mechanical strain, and third, prevention of that state of the tissues in the arterial walls which increases their receptivity to plasma lipids or prevention of that state of the blood which leads to abnormal precipitability of its lipids.

Treatment to reduce hyperlipemia consists in treatment of the underlying disease causing it. Insulin and high carbohydrate diets reduce it in diabetics along with improvement in the diabetes itself. The hyperlipemia of nephrosis disappears with spontaneous remission of the disease. Although Epstein⁵⁸ believed that large doses of thyroid might aid in reducing it, Farr and I¹⁰ were unable to find any regular effect of it on the plasma lipids of seven nephrotic patients. We concluded that whatever value thyroid substance might have in the treatment of nephrosis did not rest in its action on the hyperlipemia. Diets in which the fat has been reduced to minimal amounts yet adequate in calories and vitamins have also proved of no value in reducing nephrotic hyperlipemia. Thus until we know more about the mechanism of hyperlipemia itself, treatment must be directed toward the disease with which it is associated.

The second factor, mechanical strain, may be attacked a little more hopefully, but these means will not be discussed here.

The third factor, tissue receptivity or altered precipitability of lipids from plasma has only been combated in animals suffering from atherosclerosis experimentally produced. In proper dosage iodides, thiocyanate and other substances prevent the formation of atheromatous lesions but once the lesions are formed they do not appear to influence the rate or nature of the involution of these lesions.⁵⁹ Thyroid feeding does not accelerate the removal of cholesterol from experimental intracutaneous deposits in rabbits (Zon⁶⁰). No evidence is at hand to decide whether feeding of iodine to man is of any value. Time-honored clinical practice sanctions its use once sclerosis has developed. Whether it is valuable in preventing it is not known. Dungel⁶¹ believes that the low thyroid weight and the extremely low incidence of atherosclerosis in Iceland are probably due to the abundance of iodine in food, soil and air. This interesting observation patently needs further investigation.

Addendum: Since the manuscript has gone to press a fine paper from the pens of Drs. Weinhouse and Hirsch has appeared (Arch. Path., 1940, xxix, 31). They show that the proportion of individual lipid constituents in the intima and in the simple fatty deposits of the intima corresponds closely with those reported for these substances in blood plasma. It is suggested that the lipid deposits are the result of non-selective infiltration from plasma.

BIBLIOGRAPHY

1. ASCHOFF, L.: Virchow's Lehre von den Degenerationen (passiven Vorgängen) und ihre Weiterentwicklung, Virchow's Arch. f. path. Anat., 1921, ccxxxv, 152-185.
2. ASCHOFF, L.: Lectures on pathology, 1924, Paul B. Hoeber, Inc., New York.
3. BLOOR, W. R.: Lipemia, Jr. Biol. Chem., 1921, xlix, 201-227.
4. CORWIN, W. C.: Experimental hypercholesteremia in dogs, Arch. Path., 1938, xxvi, 456-462.
5. FLOCK, E. V., CORWIN, W. C., and BOLLMAN, J. L.: Sustained hyperlipemia of dietary origin in the dog, Am. Jr. Physiol., 1938, cxxiii, 558-565.
6. ALLEN, F. M.: (a) Experimental studies in diabetes. Series IV. Lipemia. 2. The production of diabetic lipemia in animals, and observations on some possible etiologic factors, Jr. Metab. Res., 1922, ii, 219-298. (b) Observations in the terminal state of a case of hepatic cirrhosis, Am. Jr. Med. Sci., 1919, clviii, 307-312.
7. NEWBURGH, L. H., and MARSH, P. L.: Further observations on the use of a high fat diet in the treatment of diabetes mellitus, Arch. Int. Med., 1923, xxxi, 455-490.
8. MARSH, P. L., and WALLER, H. G.: The relation between ingested fat and the lipemia of diabetes mellitus, Arch. Int. Med., 1923, xxxi, 63-75.
9. WISHART, M. B.: Experimental studies in diabetes. Series IV. Lipemia. 1. Analyses of blood lipoids in diabetic animals and patients, Jr. Metab. Res., 1922, ii, 198-217.
10. PAGE, I. H., and FARR, L. E.: Influence of high and low fat diets and thyroid substance on plasma lipids of nephrotic patients, Jr. Clin. Invest., 1936, xv, 181-191.
11. RABINOWITCH, I. M.: Arteriosclerosis in diabetes. I. Relationship between plasma cholesterol and arteriosclerosis. II. Effects of the high carbohydrate-low caloric diet, ANN. INT. MED., 1935, viii, 1436-1474.
12. SCHÖNHEIMER, R., and RITTENBERG, D.: The application of isotopes to the study of intermediary metabolism, Science, 1938, lxxxvii, 221-226.

13. PAGE, I. H., KIRK, E., and VAN SLYKE, D. D.: Plasma lipids in essential hypertension, *Jr. Clin. Invest.*, 1936, xv, 109-113.
14. KIRK, E., PAGE, I. H., and VAN SLYKE, D. D.: Gasometric micro-determination of lipids in plasma, blood cells, and tissues, *Jr. Biol. Chem.*, 1934, cvi, 203-234.
15. ALVAREZ, C., and NEUSCHLOSZ, S. M.: Untersuchungen über das Blutcholesterin bei arteriellem Hochdruck, *Klin. Wchnschr.*, 1931, x, 244-247.
16. HOLDEN, R. F., JR.: Plasma cholesterol saturation in patients with hypertension. With a note on preparation of glass filters for micro-filtration of cholesterol digitonide, *Jr. Clin. Invest.*, 1937, xvi, 763-765.
17. MEDVEI, C. V.: Zur Frage des Blutcholesterins bei arteriellem Hochdruck, *Klin. Wchnschr.*, 1932, xi, 414-416.
18. LANDÉ, K. E., and SPERRY, W. M.: Human atherosclerosis in relation to the cholesterol content of the blood serum, *Arch. Path.*, 1936, xxii, 301-312.
19. GIBBS, C. F. B., BUCKNER, E., and BLOOR, W. R.: The cholesterol to cholesterol ester ratio in the plasma of diabetics with advanced arteriosclerosis, *New Eng. Jr. Med.*, 1933, ccix, 384-386.
20. WHITE, P.: Diabetes in children, *Bull. New York Acad. Med.*, 1934, x, 347-357.
21. ANITSCHKOW, N.: Über die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose, *Beitr. z. path. Anat. u. z. allg. Path.*, 1912, lvi, 379-404.
22. LEARY, T.: Experimental atherosclerosis in the rabbit compared with human (coronary) atherosclerosis, *Arch. Path.*, 1934, xvii, 453-492.
23. MENSCHICK, W., and PAGE, I. H.: Über die Resorbierbarkeit des unbestrahlten Ergosterins. Ein Beitrag zur Methodik der quantitativen Ergosterinbestimmung, *Ztschr. f. physiol. Chem.*, 1932, ccxi, 246-252.
24. SCHÖNHEIMER, R., and DAM, H.: Über Ergosterin-Resorption bei der legenden Henne, *Ztschr. f. physiol. Chem.*, 1932, ccxi, 241-245.
25. YUASA, D.: Über experimentelle Cholesterinkrankheit bei Omnivoren, *Beitr. z. path. Anat. u. allg. Path.*, 1928, lxxx, 570.
26. MENSCHICK, W., and PAGE, I. H.: Der Abbau des Cholesterins durch den tierischen Organismus; Bilanzversuche an Carnivoren bei starker Cholesterinfütterung, *Ztschr. physiol. Chem.*, 1933, ccxviii, 95-103.
27. GAMBLE, J. L., and BLACKFAN, K. D.: Evidence indicating a synthesis of cholesterol by infants, *Jr. Biol. Chem.*, 1920, xlii, 401-409.
28. CHANNON, H. J.: Cholesterol synthesis in the animal body, *Biochem. Jr.*, 1925, xix, 424-432.
29. PAGE, I. H., and MENSCHICK, W.: The destruction of cholesterol by the animal organism, *Jr. Biol. Chem.*, 1932, xcvi, 359-368.
30. SCHOENHEIMER, R., and BREUSCH, F.: Synthesis and destruction of cholesterol in the organism, *Jr. Biol. Chem.*, 1933, ciii, 439-448.
31. PAGE, I. H., KIRK, E., LEWIS, W. H., THOMPSON, W. R., and VAN SLYKE, D. D.: Plasma lipids of normal men at different ages, *Jr. Biol. Chem.*, 1935, cxi, 613-639.
32. OBERNDORFER: Beiträge zur Frage der Lokalisation atherosklerotischer Prozesse in den peripheren Arterien, *Deutsch. Arch. f. klin. Med.*, 1911, cii, 515-519.
33. MOON, V. H.: Atheromatous degeneration of the arterial wall; the result of a hydrodynamic mechanism, *Arch. Path.*, 1927, iii, 404-408.
34. MURATA, M., and KATAOKA, S.: Einfluss der Kastration auf die experimentelle alimentäre Atherosklerose, *Trans. Japan Path. Soc.*, 1917, vii, 27. Experimentelle Atherosklerose und Schilddrüsenfütterung, *Trans. Japan Path. Soc.*, 1918, viii, 221.
35. LIEBIG, H.: Die Beeinflussung der experimentellen Atherosklerose durch Jodbehandlung, *Arch. f. exper. Path. u. Pharmakol.*, 1930, clix, 265-274.
36. TURNER, K. B., and KHAYAT, G. B.: Studies on the prevention of cholesterol atherosclerosis in rabbits. II. The influence of thyroidectomy upon the protective action of potassium iodide, *Jr. Exper. Med.*, 1933, lviii, 127-135.

37. PAGE, I. H., and BERNHARD, W. B.: Cholesterol-induced atherosclerosis; its prevention in rabbits by the feeding of an organic iodine compound, *Arch. Path.*, 1935, xix, 530-536.
38. WOTTSCHALL, B.: Ueber den Jodgehalt des Blutes nach Jodkali und Dijodyl-Darreichung, *Ztschr. f. d. ges. exper. Med.*, 1927, liv, 123-130.
39. MALISOFF, W. M.: Prevention of atherosclerosis in rabbits. I. Administration of potassium thiocyanate, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 356-358.
40. STRAUSS, L. H.: Inhibition of experimental arteriosclerosis by potassium iodide and colloidal silicic acid, *Ztschr. f. d. ges. exper. Med.*, 1936, xcvi, 603-610.
41. THIERSCH, H.: The effect of garlic on the experimental cholesterol arteriosclerosis of rabbits, *Ztschr. f. d. ges. exper. Med.*, 1936, xcix, 473-477.
42. HUBER, M. J., BROWN, G. O., and CASEY, A. E.: Prevention of cholesterol arteriosclerosis in the rabbit by use of pancreatic extract (lipocaic), *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvii, 441-445.
43. BAUMANN, C. A., and RUSCH, H. P.: Effect of choline on atherosclerosis in the rabbit aorta, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 647-651.
44. STEINER, A.: Effect of choline on production of experimental atherosclerosis in rabbits, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 231-233.
45. EBERHARD, T. P.: Effect of alcohol on cholesterol-induced atherosclerosis in rabbits, *Arch. Path.*, 1936, xxi, 616-627.
46. ASCHOFF, L.: Atherosklerose und andere Sklerosen des Gefäßsystems, *Beihefte z. med. Klin.*, 1908, iv, 1.
47. WINDAUS, A.: Über den Gehalt normaler und atheromatöser Aorten an Cholesterin und Cholesterinestern, *Ztschr. physiol. Chem.*, 1910, lxxvii, 174-176.
48. SCHÖNHEIMER, R.: Zur Chemie der gesunden und der atherosklerotischen Aorta, *Ztschr. physiol. Chem.*, 1928, clxxvii, 143-157.
49. MEEKER, D. R., and JOBLING, J. W.: A chemical study of arteriosclerotic lesions in the human aorta, *Arch. Path.*, 1934, xviii, 252-257.
50. LEHNHERR, E.: Arteriosclerosis and diabetes mellitus, *New Eng. Jr. Med.*, 1933, ccviii, 1307-1313.
51. ZEEK, P. M.: A chemical analysis of atherosclerotic lesions in human aortas, *Am. Jr. Path.*, 1936, xii, 115-128.
52. KLOTZ, O.: Studies upon calcareous degeneration. I. The process of pathological calcification, *Jr. Exper. Med.*, 1905, vii, 633-675.
53. WELLS, H. G.: Calcification and ossification, *Arch. Int. Med.*, 1911, vii, 721-753.
54. BALDAUF, L. K.: The chemistry of atheroma and calcification (aorta), *Jr. Med. Res.*, 1906, xv, 355-361.
55. PAGE, I. H., and MENSCHICK, W.: Spektrographischer Nachweis eines Begleiters des Cholesterins aus verkalkten Aorten, *Die Naturwissenschaften*, 1930, xviii, 585-586.
56. HEILBRON, I. M., MORTON, R. A., and SEXTON, W. A.: Studies in the sterol group. Part I. The absorption spectra of some cholesterol derivatives, *Jr. Am. Chem. Soc.*, 1928, i, 47-51.
57. SCHÖNHEIMER, R., RITTENBERG, D., and GRAFF, M.: Deuterium as an indicator in the study of intermediary metabolism. IV. The mechanism of coprosterol formation, *Jr. Biol. Chem.*, 1935, cxi, 183-192.
58. EPSTEIN, A. A.: Further observations on the nature and treatment of chronic nephrosis, *Am. Jr. Med. Sci.*, 1922, clxiii, 167-186.
59. MEEKER, D. R., KESTEN, H. D., and JOBLING, J. W.: Effect of iodine on cholesterol-induced atherosclerosis, *Arch. Path.*, 1935, xx, 337-342.
60. ZON, L.: Effect of thyroid feeding on the removal of cholesterol, *Arch. Path.*, 1939, xxvii, 888-894.
61. DUNGAL, N. P.: Weight of thyroid gland and athero-sclerosis, *Lancet*, 1936, i, 1354-1356.

62. CORCORAN, A. C., and RABINOWITCH, I. M.: A study of the blood lipoids and blood protein in Canadian eastern arctic Eskimos, *Biochem. Jr.*, 1937, xxxi, 343-348.
63. TOLSTOI, E.: The effect of an exclusive meat diet on the chemical constituents of the blood, *Jr. Biol. Chem.*, 1929, lxxxiii, 753-758.
64. KAPLAN, A., and CHAIKOFF, I. L.: Liver lipids in completely depancreatized dogs maintained with insulin, *Jr. Biol. Chem.*, 1935, cviii, 201-216.
65. CORCORAN, A. C., and RABINOWITCH, I. M.: Unpublished observation.
66. CHAIKOFF, I. L., and KAPLAN, A.: The influence of the ingestion of raw pancreas upon the blood lipids of completely depancreatized dogs maintained with insulin, *Jr. Biol. Chem.*, 1935, cxii, 155-165.

THE CHOLESTEROL CONTENT OF THE RENAL ARTERIES AND OF THE THORACIC AORTA IN RELATION TO HYPERTENSION AND VASCULAR PATHOLOGY *

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THE investigations of Goldblatt¹ have focused attention on renal ischemia as one of the etiological agents responsible for hypertension. Ample clinical confirmation of this concept has appeared in the recent literature²⁻¹⁵ and not a few of the cases cited are counterparts of Goldblatt's experiments on dogs and monkeys. It must be conceded, however, that necropsies on most patients with essential hypertension fail to reveal gross renal ischemia. In 1939, Christian, Schlesinger and Myers¹⁶ showed that the perfusion flow through kidneys obtained at postmortem examinations of patients having essential hypertension was decidedly less than the flow through kidneys of persons with normal blood pressure and that the decrease in total perfusion flow occurred without there being any decrease in kidney weight. They observed only a slightly higher incidence of gross atherosclerosis of the renal arteries in individuals with hypertension than in those with normal blood pressure. Blackman¹⁷ reported that the main renal arteries in 43 of 50 patients with essential hypertension had atherosclerotic plaques narrowing their lumens. One or both of the main renal arteries were markedly stenosed in 27 cases. A degree of atherosclerosis and stenosis of the main renal arteries comparable to that seen in the cases of hypertension was found in only five of 50 patients with normal blood pressure.

The present study was carried out to determine if any relationship existed between the cholesterol content of the renal arteries and the presence or absence of hypertension. This investigation was extended to include the simultaneous determination of the cholesterol content of the thoracic aorta. The results were then correlated with clinical findings and vascular pathology.

Schönheimer,^{18, 19} among others,^{20, 21, 22, 23, 24, 25} has shown that atherosclerotic lesions in the aorta are particularly rich in cholesterol and that a direct relationship exists between the concentration of cholesterol in the aorta and the amount of atherosclerosis present. It appears valid to assume, therefore, that the same relationship is true for the renal arteries.

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MATERIAL AND METHODS

Twenty-four renal arteries and 37 thoracic aortas were obtained from 37 consecutive necropsies. The adventitia was carefully stripped from the arteries, the vessels opened by longitudinal incision, and the blood removed by washing in cold water. The arteries were then dried to constant weight at 60° C. The dried vessels were then broken into small pieces and the lipoids were removed by two extractions with hot 95 per cent ethyl alcohol and one with boiling ethyl ether (approximately 50 c.c. of the solvent were used each time). The combined extracts were evaporated to dryness at 60° C. Cholesterol was removed from the dried extracts by chloroform and then determined colorimetrically on a satisfactory aliquot by a modified Liebermann-Burchard reaction.²⁶ The right and left renal arteries were analyzed together so that the values represent the average cholesterol content of both vessels. The results are expressed in milligrams of cholesterol per 100 grams of dry artery.

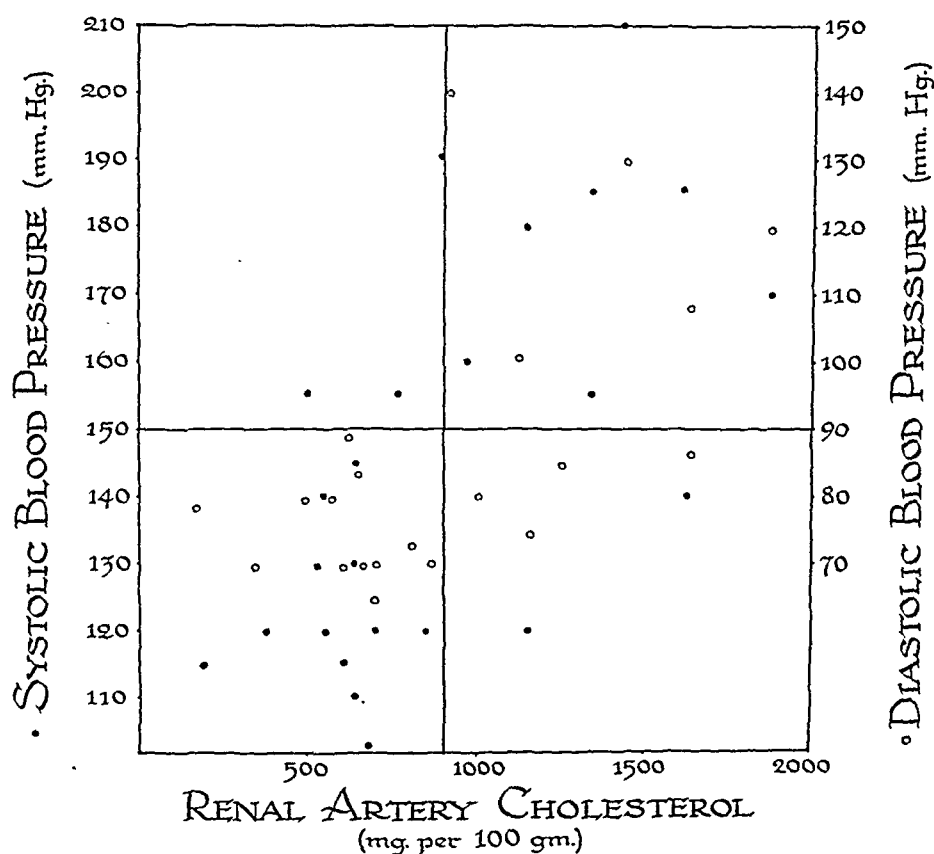


FIG. 1. Relation of renal artery cholesterol to systolic and diastolic blood pressure.

RESULTS

Figure 1 demonstrates the relationship between the cholesterol content of the renal arteries and the average systolic and diastolic blood pressure.

This figure demonstrates that a concentration of cholesterol in the renal arteries of over 900 mg. per 100 grams of dry vessel is frequently associated with a systolic blood pressure of over 150 mm. of Hg and diastolic pressure of over 90 mm. of Hg. Patients with low concentrations of cholesterol in the renal arteries rarely manifest hypertension.

Table 1 shows the average cholesterol content of the aortas and renal arteries in 19 non-hypertensive and in 12 hypertensive individuals grouped according to age. After 20 years, there is a tendency for a progressive increase in the cholesterol content of the thoracic aorta which, from the limited data available, would appear to be more pronounced in patients with hypertension than in those with normal blood pressure. The concentration of cholesterol in the renal arteries in subjects with normal blood pressure is remarkably constant throughout life. Thus, the ratio of cholesterol deposited

TABLE I

Relation of Aortic Cholesterol and Renal Artery Cholesterol to Age in Non-Hypertensive and Hypertensive Subjects

Age Group years	Non-Hypertensive				Hypertensive			
	No. Cases	Av. Aortic Chol. mg./100 gm.	Av. Renal Art. Chol. mg./100 gm.	Aortic/Renal Art. Chol.	No. Cases	Av. Aortic Chol. mg./100 gm.	Av. Renal Art. Chol. mg./100 gm.	Aortic/Renal Art. Chol.
Less than 9	3	315	803	0.4				
10-19	1	254	201	1.3				
20-29	1	1766	645	2.7				
30-39	6	1568	704	2.2	1	1648	904	1.8
40-49	3	1626	625	2.6	2	1893	820	2.3
50-59	3	2279	691	3.3	2	2413	1659	1.4
60-69	1	1832	502	3.6	3	2958	1569	1.8
70-79	1	3798	798	4.8	4	4197	2111	1.9

in the aorta to that in the renal arteries increases with age in non-hypertensive individuals. In patients with hypertension, the increased concentration of cholesterol in the renal arteries is reflected in a fairly uniform ratio of cholesterol in the aorta to that in the renal arteries irrespective of the age period.

Table 2 shows the relationship between the cholesterol content of the renal arteries and kidney pathology as revealed by microscopic study. This table demonstrates that high concentrations of cholesterol in the renal arteries are accompanied by: (1) alterations in the vascular and parenchymatous renal components, (2) impairment of renal function, and (3) urinary changes indicative of renal pathology. Renal arteries low in cholesterol are rarely associated with such findings.

Table 3 indicates the heart weight, microscopic pathology of the coronary arteries, and electrocardiographic findings in 37 patients with and without hypertension grouped according to increasing concentrations of cholesterol in the thoracic aorta. This table shows that little or no relationship exists

TABLE II
Relation of Renal Artery Cholesterol to Renal Pathology

Renal Art. Chol. mg./100 gm.	Case No.	Renal Pathology			Renal Function	Urine Analysis
		Arterioles*	Glomerulus	Tubules		
200-500	5	Normal	Congestion	Cloudy swelling	Normal	Normal
	22	Normal	Congestion	Cloudy swelling	Normal	Normal
500-800	4	Normal	Normal	Normal		Tr. prot.; rare cast; rare r.b.c.
	10	+	Normal	Cloudy swelling	Normal	Normal
	12	+	Acute pyelonephr.	Acute pyelonephr.	Normal	Many w.b.c.
	13	Normal	Normal	Cloudy swelling	Normal	Normal
	14	Normal	Normal	Cloudy swelling	Normal	Normal
	17	Normal	Congestion	Cloudy swelling	Normal	Normal
	24	Normal	Normal	Cloudy swelling	Normal	Tr. prot.
	29	Normal	Normal	Normal		Normal
	31	Normal	Normal	Normal		Normal
	33	Normal	Normal	Normal	Normal	Tr. prot.
	34	Normal	Normal	Normal	Normal	Tr. prot.
	35	Normal	Normal	Cloudy swelling		
	36	Normal	Normal	Cloudy swelling	Normal	+ prot.
800-1100	2	+++	Normal	Normal	Normal	
	3	Normal	Normal	Normal		
	7	Normal	Normal	Cloudy swelling	Normal	Tr. prot.; rare cast
	8	++++	Hyalinization	Cloudy swelling		Tr. prot.
	11	+	Normal	Cloudy swelling	Normal	Normal
	27	Normal	Normal	Cloudy swelling	Normal	Normal
1100-1400	6	Normal	Normal	Normal		Normal
	19	Normal	Normal	Cloudy swelling	Normal	Normal
	28	+++	Acute nephritis	Swelling, necrosis	Mod. impaired	++ prot.; many casts and r.b.c.
	30	+++	Hyalinization	Cloudy swelling	Sl. impaired	+ prot.
1400-1700	18	++	Hyalinization	Cloudy swelling	Sl. impaired	+++ prot.; rare casts and r.b.c.
	21	+++	Hyalinization	Cloudy swelling, fatty degener.		
	25	+++	Chr. pyelonephr.	Cloudy swelling	Severely impaired	++ prot.; many r.b.c.
1700 and over	20	+++	Hyalinization	Atrophy		Tr. prot.
	23		Chr. pyelonephr.	Atrophy		Tr. prot.; many casts; occasional r.b.c.
	32	++	Normal	Normal	Mod. impaired	

* + indicates slight intimal thickening; ++ moderate intimal thickening and narrowing; +++ severe intimal thickening, narrowing and hyalinization; ++++ necrotizing arteriolitis.

between heart weight and the amount of cholesterol deposited in the aorta. On the other hand, high concentrations of cholesterol in the aorta are frequently accompanied by pronounced atherosclerotic changes in the coronary arteries. This is further substantiated by electrocardiographic changes indicative of myocardial disease.

DISCUSSION

Of fundamental importance is the question whether the increased deposition of cholesterol in the main renal arteries is a primary manifestation of hypertension or whether it represents a secondary effect of the increased intravascular tension. Recently, Davis and Klainer²⁷ surmised that atherosclerosis, by virtue of its irregular distribution, may involve the renal arteries, thereby producing renal ischemia. This concept is interesting but not proved. Further studies are being performed in this laboratory in an attempt to solve this problem. If it should be shown that in hypertensive

TABLE III

Relation of Cholesterol Content of Thoracic Aorta to Cardiac Pathology.

Aortic Chol. mg./100 gm.	Case No.	Age Years	Heart		
			Weight Grams	Coronary Arteries	Electrocardiogram
100-600	1	1 mo.	25	Normal	
	3	3 mos.		Normal	
	4	1½	70	Normal	
	5	12	165	Normal	
	27	3½ mos.	30	Normal	
600-1100	11	51	310	Normal	
	13	37	260	Slight intimal thick- ening	
	17	45	260	Sl. atheromatosis	
	22	34	330	Normal	
	26	22	170	Normal	
	28	46	270	Atheromatous plaques without narrowing	Fast rate only
1100-1600	6	65	430	Sl. atheromatosis	
	7	31	Enlarged	Normal	
	14	30		Normal	
	15	33	250	Normal	
	16	35	450	Sl. atheromatosis	Myocardial damage
	33	42	350	Normal	
	37	54	390	Few atherom. plaq.	
1600-2100	8	38	370	Atherom. plaques	Myocardial damage
	9	64		Normal	
	23	57	430	Mod. atheromatosis	Myocardial damage
	31	66	330	Atherom. plaques	Auricular flutter
	36	28	240	Normal	
2100-2600	12	57	625	Marked arterioscl.	Left axis dev.
	19	37	270	Normal	
	24	47	320	Normal	
2600-3100	25	52	440	Mod. atheromatosis	Myocardial damage
	34	49	Enlarged	Mark. atheromatosis with narrowing	Myocardial damage
	35	32	Enlarged	Mark. intim. thick.	Myocardial damage
3100 and over	2	75	470	Mod. arterioscl.	
	10	79	320		
	18	69	600	Mod. atheromatosis	Auricular fibril.
	20	73		Marked arterioscl.	
	21	65		Marked arterioscl. with narrowing	
	29	57	430	Many atherom. plaq.	
	30	73	510	Mod. atheromatosis	Left b.b. block Myocardial damage
	32	74	290	Marked arterioscl.	

individuals the degree of deposition of cholesterol in the renal arteries is considerably greater than in other arteries of approximately equal caliber, it may be argued that atherosclerosis of the renal arteries is one of the primary factors producing renal ischemia with resultant hypertension.

Schönheimer^{18, 19} has observed that the cholesterol content of the aorta increases with age; the present studies are confirmatory. Limited data have been presented to indicate that the deposition of cholesterol in the thoracic aorta in patients with hypertension may be more pronounced than in the non-hypertensive individuals for the same age period. The question arises, therefore, whether cholesterol is deposited in excess simultaneously in the thoracic aorta and main renal arteries of individuals prior to the development of hypertension, or whether the increased concentration of cholesterol in the aorta represents a secondary infiltration with this lipid due to high intra-arterial tension. Obviously, a large series of chemical analyses (or pathologic studies) and a correlation of the cholesterol values of these vessels with the duration and degree of hypertension would be necessary before this question could be answered satisfactorily.

Moritz and Oldt²⁸ have shown that a correlation exists between renal arteriolar sclerosis and hypertension. They state that "the renal arteriolar sclerosis in man seems to have the same functional effect as the silver clamp around the main arteries of dogs." Their work was based solely on a study of the renal arterioles; the main renal arteries were not investigated. The present studies emphasize the parallelism existing between the cholesterol content of the renal arteries and the extent of pathologic changes observed microscopically in the arterioles of the kidney and other renal components. The main renal arteries, therefore, in addition to the renal arterioles, are the seat of vascular constriction.

SUMMARY AND CONCLUSIONS

1. In subjects with normal blood pressure, the cholesterol content of the main renal arteries was fairly constant throughout life, averaging approximately 700 mg. per 100 grams of dry artery.

2. In patients with hypertension, the cholesterol content of the main renal arteries was frequently increased. Values from 900 mg. to 2,000 mg. per 100 grams of dry artery were not uncommon.

3. The cholesterol content of the thoracic aorta was found to increase with age. The deposition of cholesterol in the thoracic aorta appeared to be greater in patients with hypertension than in subjects with normal blood pressure for the same age period.

4. The ratio of the concentration of cholesterol in the thoracic aorta to that in the main renal arteries showed a progressive increase with age in subjects with normal blood pressure. This ratio remained relatively constant in patients with hypertension, due mainly to the high concentration of cholesterol in the renal arteries.

5. The degree of pathologic changes in the kidney, as revealed by microscopic studies of the arterioles, glomeruli and tubules, was found to vary directly with the concentration of cholesterol in the main renal arteries.

6. No consistent relationship was observed between the heart weight and the concentration of cholesterol in the thoracic aorta.

7. The degree of pathologic changes in the heart as revealed by microscopic studies of the coronary arteries and by electrocardiographic recordings was found to vary directly with the concentration of cholesterol in the thoracic aorta.

CASE PROTOCOLS

Case 1. Male, one month. Persistent vomiting since birth. Gastrointestinal roentgen-rays revealed intestinal obstruction at ileocecal junction. Laparotomy performed with resection of Meckel's diverticulum. Postoperatively, patient developed paralytic ileus. Death followed after re-operation for ileostomy. *Necropsy:* Acute serofibrinous peritonitis; congenital partial stenosis of ileum.

Case 2. Male, 75 years. Urinary frequency and dysuria for one year. Physical examination revealed obesity, enlarged heart and marked prostatic enlargement. Blood pressure 160 mm. mercury systolic over 80 mm. diastolic. Cystoscopic examination disclosed a fungating growth involving the posterior urethra and adjacent bladder wall. Radon seeds were implanted into the prostate four days later through a suprapubic cystotomy. On the twenty-eighth hospital day, patient suddenly collapsed and died soon thereafter. *Necropsy:* Carcinoma of the prostatic gland with metastases to retroperitoneal lymph nodes and bladder; pulmonary embolism.

Case 3. Male, three months. Acute purulent otitis media at one month of age followed by bronchopneumonia, empyema (*Staphylococcus aureus*), and *Staphylococcus aureus* septicemia. Thoracotomy and bacteriophage therapy were of no avail. *Necropsy:* Bronchopneumonia with multiple lung abscesses and empyema.

Case 4. Male, one and one-half years. Recurrent vomiting for six months; cyanosis for three days. Febrile course. Patient died on third hospital day in spite of supportive measures. *Necropsy:* Bronchopneumonia.

Case 5. Female, 12 years. Personality changes, loss of memory, defective speech, and unsteady gait for seven weeks. Physical examination revealed sluggishness, irregular pupils, left facial palsy and bilateral chorioretinal degeneration with beginning optic atrophy. Three days after admission, marked ataxia of upper extremities and bilateral papilledema were observed. Lumbar puncture: clear cerebrospinal fluid under increased pressure; negative Wassermann; normal Queckenstedt. Afebrile course until a few hours before exitus on the sixteenth hospital day. Temperature rose as patient became comatose. Normal blood pressure. *Necropsy:* Non-luetic encephalitis.

Case 6. Male, 65 years. Right upper quadrant pain and weight loss of 15 pounds over a period of three months. Physical examination revealed a cystic, slightly tender mass in right side of abdomen extending into pelvis. Blood pressure 154 mm. mercury systolic and 86 mm. diastolic. Laparotomy disclosed right renal neoplasm. Patient developed postoperative shock. *Necropsy:* Teratoblastic tumor of right kidney.

Case 7. Male, 31 years. History not available because patient was admitted in moribund state. Physical examination revealed cardiac enlargement and apical systolic murmur transmitted to axilla. Blood pressure normal. Blood culture positive for *Streptococcus viridans*. *Necropsy:* Subacute bacterial endocarditis of mitral valve.

Case 8. Male, 38 years. Hypertension for six years. Physical examination revealed enlarged heart, systolic murmur at apex of heart, and angiosclerosis of fundi graded one plus. Blood pressure 210 mm. mercury systolic, 120 mm. diastolic. Right nephro-omentopexy was performed in May 1938. Two weeks postoperatively patient developed severe pain in region of umbilicus which persisted despite all medication until day of death two and one-half months after operation. *Necropsy:* Dissecting ruptured aneurysm of celiac axis artery.

Case 9. Female, 64 years. A papillary adenocarcinoma of the transverse colon was resected in 1934. In April 1938, patient developed bilateral sciatic neuritis which failed to respond to all forms of treatment including nerve block. Normal blood pressure. Left lower lobe pneumonia ensued on fifth hospital day. *Necropsy:* Bronchopneumonia, left lower lobe. No evidence of metastatic malignancy.

Case 10. Female, 79 years. Pain, unremitting in character, of both legs and left arm for five months. Physical examination revealed marked pain on motion of extremities and systolic murmurs at apex and base of heart. Blood pressure normal. Patient died in coma on forty-seventh hospital day. *Necropsy:* Lymphosarcoma (reticulum cell type) of ileum with metastases to mediastinal and retroperitoneal lymph nodes.

Case 11. Female, 51 years. Admitted in 1936 for panhysterectomy. Pathologic diagnosis: Adenocarcinoma of uterus. Readmitted in 1938 because of asthenia and progressive weight loss. Physical examination revealed marked pallor, ascites and peripheral edema. Blood pressure normal. *Necropsy:* Metastatic adenocarcinoma of uterus to retroperitoneal and pelvic lymph nodes.

Case 12. Male, 57 years. Fever of unknown etiology and generalized muscular pains for three months. Physical examination revealed pallor and loud systolic murmur at apex of heart. Blood cultures consistently positive for a small gram-negative rod which grew scantily. In form, the organism resembled members of the para-influenzal group, but culturally it belonged to the paratyphoid group. Complete identification was not established. Patient died on fifty-fifth hospital day. *Necropsy:* Subacute bacterial endocarditis due to an unidentified organism.

Case 13. Male, age 37 years. Chief complaints were cough, pain in right chest, and dyspnea. Physical examination revealed signs of consolidation of right middle and right lower lobes. Type V pneumococci were isolated from blood and sputum. Serum therapy and sulfanilamide were employed. Pneumonia extended to involve left lower lobe. Blood pressure normal. *Necropsy:* Atypical lobar pneumonia.

Case 14. Male, 30 years. Jaundice for six months; tarry stools and hematemesis for two days. Physical examination revealed marked icterus, hepatomegaly and splenomegaly. Normal blood pressure. On the third hospital day patient developed severe gastric hemorrhage and died two days later. *Necropsy:* Portal cirrhosis of liver (hypertrophic stage); ruptured esophageal varix.

Case 15. Female, 33 years. Recurrent attacks of toxic dermatitis with necrosis of skin for six years. Skin biopsies revealed vesicular and hemorrhagic chronic dermatitis. In June 1938, progressive swelling of neck was noted. Basal metabolic rate was +17 per cent. Normal blood pressure. Subtotal thyroidectomy performed because of chronic thyroiditis. Developed bronchopneumonia postoperatively. *Necropsy:* Lymphosarcoma, generalized.

Case 16. Female, 35 years. Rheumatic heart disease since eight years of age. Chief complaints were purulent discharge from right ear, fever and general malaise. Physical examination revealed mitral stenosis and insufficiency and aortic stenosis. Blood culture positive for *Streptococcus viridans*. Blood pressure normal. On thirty-third hospital day, patient developed left hemiplegia. Splenic, renal and pulmonary infarcts occurred during hospitalization. *Necropsy:* Subacute bacterial endocarditis of mitral and aortic valves; rheumatic heart disease.

Case 17. Male, 45 years. Progressive constipation and weight loss for nine months. Physical examination revealed mass in left rectal wall. Blood pressure normal. Biopsy specimen revealed adenocarcinoma of rectum. Admitted for resection. At operation, extensive pelvic carcinomatosis was found. *Necropsy:* Adenocarcinoma of rectum; bronchopneumonia; secondary intestinal obstruction.

Case 18. Male, 69 years. Edema of ankles, dyspnea, and weight gain of 40 pounds in past two months. Physical examination revealed obesity, cyanosis, dyspnea,

orthopnea, venous engorgement of neck veins, sclerosis of peripheral blood vessels, bilateral pleural effusion, marked cardiac enlargement, systolic murmur at the apex of the heart, auricular fibrillation, hepatomegaly and anasarca. Blood pressure 185 mm. mercury systolic, 108 mm. diastolic. Patient died on the eighth hospital day. *Necropsy*: Arteriosclerosis, generalized; bronchopneumonia, generalized; hydrothorax, bilateral; marked cardiac hypertrophy.

Case 19. Male, 37 years. Hemorrhage from socket following extraction of tooth. Physical examination revealed pallor and systolic murmur at apex of heart. Blood pressure normal. Hemoglobin 30 per cent, red blood cells 1,250,000, leukopenia (1100) with 10 per cent polymorphonuclear neutrophils and 87 per cent lymphocytes. Necrosis of the left mandible developed. Metamyelocytes were later found in peripheral blood smears. Course downhill in spite of repeated blood transfusions. *Necropsy*: Chronic lymphatic leukemia, aleukemic type; necrotizing gingivitis and stomatitis; bronchopneumonia.

Case 20. Female, 73 years. History not available because patient was admitted in moribund state. Physical examination revealed signs of shock with deep and labored respirations. Death occurred half an hour after admission. *Necropsy*: Thrombosis of right coronary artery with myomalacia of the posterior wall of the left ventricle and posterior part of the interventricular septum. (Although no history of hypertension was obtained, this patient was considered to have had hypertension because of left ventricular hypertrophy.)

Case 21. Male, 65 years. Cough and hemoptysis for two years; marked recent weight loss and asthenia. Physical examination revealed consolidation in left lower lobe. Blood pressure 150 mm. mercury systolic, 90 mm. diastolic. On the seventh hospital day, convulsions of left side of body occurred with subsequent clouding of sensorium. Cheyne-Stokes breathing ensued and patient died on the fiftieth hospital day. *Necropsy*: Bronchogenic carcinoma, mixed type, of left lower lobe with metastases to regional lymph nodes and brain.

Case 22. Male, 34 years. History of vertigo, headache and drowsiness for six months. Physical examination revealed bilateral optic neuritis, exaggerated deep reflexes and anosmia of left nostril. Blood pressure normal. Encephalogram normal. Discharge diagnosis was probable brain tumor. Readmitted because of right-sided convulsion. Ventriculogram performed with release of bloody fluid. Following ventriculogram, patient developed respiratory arrest and died. *Necropsy*: Glioblastoma multiforme, right frontal lobe; medullary herniation.

Case 23. Male, 57 years. Enlargement of neck and nervousness for one year. Basal metabolism test unsatisfactory. Physical examination revealed cardiac enlargement and adenoma of thyroid gland. Blood pressure 170 mm. mercury systolic, 120 mm. diastolic. At operation, the left lobe of the thyroid gland was enlarged about 10 times normal size and extended substernally. The left lobe was subtotally resected. Four days postoperatively, bronchopneumonia developed. *Necropsy*: Confluent bronchopneumonia, bilateral; non-toxic adenoma of thyroid gland.

Case 24. Female, 47 years. Chronic alcoholism of long standing. Chief complaints were nausea and vomiting. Physical examination revealed pallor, icterus, systolic murmur at base of heart, ascites and hepatomegaly. Blood pressure normal. Patient died of cholemia on the twenty-eighth hospital day. *Necropsy*: Biliary cirrhosis of liver; chronic cholangitis; aortic atherosclerosis, moderate.

Case 25. Female (colored), 52 years. Admitted for congestive heart failure. Arterial hypertension for six years. Physical examination revealed tachypnea, engorgement of neck veins, consolidation of left lower lobe, enlarged heart, systolic murmur at apical and aortic areas of heart, hard ulcerated cervix and "frozen" pelvis. Blood urea nitrogen was 120 mg. per cent. Blood pressure 194 mm. mercury systolic, 132 mm. diastolic. Patient died on the fifth hospital day. *Necropsy*: Squamous cell carcinoma of cervix with metastases to pelvic and retroperitoneal

lymph nodes obstructing right ureter; acute diffuse glomerular nephritis with bilateral healed pyelonephritis; atelectasis, partial, of both lower lobes.

Case 26. Female, 22 years. Chief complaint was abdominal pain in the left lower quadrant. Physical examination revealed tender mass in right vaginal vault. Blood pressure normal. Laparotomy disclosed right tuboövarian abscess and pelvic peritonitis. Postoperative course was stormy, being complicated by the development of a subphrenic abscess. The abscess was drained. *Necropsy:* Pelvic abscess with rectal perforation and extension to subphrenic space and pleura.

Case 27. Male, three and one-half months. Jaundice at one day of age. Admitted because of poor general development. Physical examination revealed the spleen to be enlarged three fingers'-breadth below the costal margin. Patient died on day of admission. *Necropsy:* Unsatisfactory explanation of case. Changes in liver, spleen and lymph nodes were suggestive of leukemia or obscure infection. Portal of entry of latter was unknown.

Case 28. Female, 46 years. Diabetes mellitus for 11 years; hypertension for one year. Admitted because of right upper quadrant pain, nausea and vomiting. Physical examination revealed hemorrhagic retinitis and cardiac enlargement. Blood pressure 200 mm. mercury systolic, 100 mm. diastolic. Urinalysis showed many red blood cells. Symptomatic treatment and diabetic control were carried out. Patient was discharged improved. Readmitted two months later complaining of frontal headaches and vomiting. Blood chemistry revealed nitrogen retention. Neurological examination negative. Low grade fever until one week prior to exitus when chills and septic type fever occurred. Terminally, patient showed Cheyne-Stokes respiration, pulmonary edema, and convulsions. *Necropsy:* Chronic diffuse glomerular nephritis; terminal bronchopneumonia; meningiomata (2); cholecystitis and cholelithiasis.

Case 29. Male, 57 years. Alternating constipation and diarrhea for three months. Admitted for resection of carcinoma of sigmoid colon. Obstruction of colostomy opening developed three months later, and at operation marked abdominal carcinomatosis was found. Blood pressure normal. Roentgen-ray therapy was given, but patient died on the sixth postoperative day. *Necropsy:* Adenocarcinoma of rectum with generalized abdominal metastases; cholelithiasis.

Case 30. Male, 73 years. Nocturia and urinary frequency for eight years; hematuria for two weeks. Physical examination revealed obesity, enlarged heart, sharp systolic murmur at apex of heart, pulmonary emphysema, sclerosis of peripheral blood vessels, ankle edema, varicose veins of the lower extremities, and marked prostatic hypertrophy. Blood pressure 180 mm. mercury systolic, 95 mm. diastolic. Cystoscopic examination disclosed a markedly trabeculated bladder and a necrotic papilloma on the bladder wall which was removed by electrocoagulation. Ten days after cystoscopy, a transurethral resection of the enlarged prostate was carried out. On the second postoperative day bronchopneumonia developed from which the patient failed to recover. *Necropsy:* Papillary carcinoma of the bladder; prostatic hypertrophy, benign; cholelithiasis; chronic diffuse glomerular nephritis; cardiac hypertrophy.

Case 31. Male, 66 years. Alternating diarrhea and constipation for six weeks. Physical examination revealed a non-tender, freely movable mass in left lower quadrant. Blood pressure normal. Operation: First stage Mikulicz with resection of carcinoma at rectosigmoid junction. Impure heart flutter developed on the fourth postoperative day with subsequent development of congestive failure and acute peritonitis. *Necropsy:* Adenocarcinoma of the sigmoid colon; acute diffuse peritonitis.

Case 32. Female, 74 years. Right upper quadrant pain for two months; enlargement of abdomen and jaundice for one week. Physical examination revealed cachexia, pallor, enlarged heart, large irregular liver and ankle edema. Blood pressure 150 mm. mercury systolic, 74 mm. diastolic. Course was progressively downhill and patient died on the twenty-sixth hospital day. *Necropsy:* Adenocarcinoma of the

sigmoid colon with metastases to abdominal lymph nodes and liver; cholelithiasis; arteriosclerosis, generalized.

Case 33. Female, 42 years. Irregular menses, backache and constipation for one year. Physical examination revealed marked uterine enlargement. Normal blood pressure. Laparotomy disclosed an intramural fibroid, chronic salpingitis and pelvic adhesions. Hysterectomy was performed, and on the fourth postoperative day signs of intestinal obstruction developed. *Necropsy:* Acute purulent peritonitis, generalized.

Case 34. Male, 49 years. Sudden, sharp substernal pain and dyspnea occurred during straining at stool. Physical examination revealed signs of shock from which the patient failed to recover. Died 16 hours after admission. Blood pressure known to be elevated prior to admission. *Necropsy:* Dissecting aneurysm of the ascending portion of the thoracic aorta with internal rupture at beginning of the arch and external rupture into the pericardial sac.

Case 35. Male, 32 years. Weakness, headache and fever for one year. Congenital heart disease discovered at two years of age. Physical examination revealed enlarged heart and a murmur and thrill characteristic of patent ductus arteriosus. Blood pressure normal. Blood cultures repeatedly positive for *Streptococcus viridans*. Died of congestive heart failure three months after admission. *Necropsy:* Congenital heart disease, patent ductus arteriosus; subacute bacterial endocarditis with vegetations on pulmonic and aortic valves and in ductus arteriosus.

Case 36. Female, 28 years. Weakness, malaise and abdominal pain for one month. Physical examination revealed inanition, pallor and sternal tenderness. Normal blood pressure. Blood count showed normocytic anemia, leukopenia (1650) with 76 per cent lymphocytes. No abnormal white blood cells were seen. Bronchopneumonia developed on the fourteenth hospital day. *Necropsy:* Acute leukemia (immaturity of white blood cells prevented further differentiation).

Case 37. Male, 54 years. Epigastric distress and fever for three days. Physical examination revealed exquisite tenderness in epigastrium and right upper quadrant. Enlarged tender liver and mass believed to be gall-bladder were disclosed. Blood pressure 138 mm. mercury systolic, 90 mm. diastolic. At operation a ruptured empyema of the gall-bladder was found. On the twelfth postoperative day developed wound dehiscence which was resutured. Died on the following day of shock and peritonitis. *Necropsy:* Generalized peritonitis.

BIBLIOGRAPHY

1. GOLDBLATT, H.: Experimental hypertension induced by renal ischemia, Harvey Lectures, 1937-1938, p. 237, Williams and Wilkins Co., Baltimore.
2. BUTLER, A. M.: Chronic pyelonephritis and arterial hypertension, Jr. Clin. Invest., 1937, xvi, 889.
3. BARKER, N. W., and WALTERS, W.: Hypertension associated with unilateral chronic atrophic pyelonephritis: treatment by nephrectomy, Proc. Staff Meet. Mayo Clin., 1938, xiii, 118.
4. LEADBETTER, W. F., and BURKLAND, C. E.: Hypertension in unilateral renal disease, Jr. Urol., 1938, xxxix, 611.
5. BOYD, C. H., and LEWIS, L. G.: Nephrectomy for arterial hypertension, preliminary report, Jr. Urol., 1938, xxxix, 627.
6. LEITER, L.: Unusual hypertensive renal disease: 1. Occlusion of renal arteries (Goldblatt hypertension); 2. Anomalies of urinary tract, Jr. Am. Med. Assoc., 1938, cxi, 507.
7. FREEMAN, G., and HARTLEY, G., JR.: Hypertension in a patient with a solitary ischemic kidney, Jr. Am. Med. Assoc., 1938, cxi, 1159.
8. BARNEY, J. D., and SUBY, H. I.: Unilateral renal disease with hypertension, New England Jr. Med., 1939, ccxxx, 744.

9. OPPENHEIMER, B. S., KLEMPERER, P., and MOSCHKOWITZ, L.: Evidence for the Goldblatt mechanism of hypertension in human pathology, *Trans. Assoc. Am. Phys.*, 1939, liv, 69.
10. BLATT, E., and PAGE, I. H.: Hypertension and constriction of the renal arteries in man: Report of a case, *ANN. INT. MED.*, 1939, xii, 1690.
11. COHN, A. E., SCHROEDER, H. A., and STEELE, J. M.: Essential hypertension and diseases of the kidneys, *Trans. Assoc. Am. Phys.*, 1939, liv, 82.
12. BARKER, N. W., and WALTERS, W.: Hypertension and unilateral renal disease, *Jr. Am. Med. Assoc.*, 1940, cxiv, 613.
13. BARKER, N. W., and WALTERS, W.: Hypertension and chronic atrophic pyelonephritis, *Proc. Staff Meet. Mayo Clin.*, 1940, xv, 475.
14. NESBIT, R. M., and RATLIFF, R. K.: Hypertension associated with unilateral nephropathy, *Jr. Urol.*, 1940, xliii, 427.
15. SCHROEDER, H. A., and FISH, G. W.: Studies on "essential" hypertension. III. The effect of nephrectomy upon hypertension associated with organic renal disease, *Am. Jr. Med. Sci.*, 1940, cxcix, 601.
16. CHRISTIAN, H. A., SCHLESINGER, M. J., and MYERS, J. D.: A perfusion and injection study of human kidneys in relation to intravital blood pressure, *Trans. Assoc. Am. Phys.*, 1939, liv, 57.
17. BLACKMAN, S. S., JR.: Arteriosclerosis and partial obstruction of the main renal arteries in association with "essential" hypertension in man, *Bull. Johns Hopkins Hosp.*, 1939, lxxv, 353.
18. SCHÖNHEIMER, R.: Zur Chemie der gesunden und der atherosklerotischen Aorta. Ueber die quantitativen Verhältnisse des Cholesterins und der Cholesterinester, *Ztschr. f. physiol. Chem.*, 1926, clx, 61.
19. SCHÖNHEIMER, R.: Zur Chemie der gesunden und der atherosklerotischen Aorta, *Ztschr. f. physiol. Chem.*, 1928, clxxvii, 143.
20. BALDAUF, L. K.: The chemistry of atheroma and calcification (aorta), *Jr. Metab. Res.*, 1906, xv, 355.
21. WINDAUS, A.: Ueber den Gehalt normaler und atheromatöser Aorten an Cholesterin und Cholesterinester, *Ztschr. f. physiol. Chem.*, 1910, lxxvii, 174.
22. LEHNHERR, E. R.: Arteriosclerosis and diabetes mellitus, *New England Jr. Med.*, 1933, ccviii, 1307.
23. MEEKER, D. R., and JOBLING, J. W.: A chemical study of arteriosclerotic lesions in the human aorta, *Arch. Path.*, 1934, xviii, 252.
24. ZEEK, P. M.: A chemical analysis of atherosclerotic lesions in human aortas, *Am. Jr. Path.*, 1936, xii, 115.
25. LEARY, T.: Atherosclerosis: special consideration of aortic lesions, *Arch. Path.*, 1936, xxi, 419.
26. MIRSKY, I. A., and BRUGER, M.: A note on the Liebermann-Burchard color reaction for cholesterol, *Jr. Lab. and Clin. Med.*, 1932, xviii, 304.
27. DAVIS, D., and KLAINER, M. J.: Studies in hypertensive heart disease. II. The rôle of hypertension, per se, in the development of coronary sclerosis, *Am. Heart Jr.*, 1940, xix, 193.
28. MORITZ, A. R., and OLDT, M. R.: Arteriolar sclerosis in hypertensive and non-hypertensive individuals, *Am. Jr. Path.*, 1937, xiii, 679.

THE NATURE OF MALIGNANT HYPERTENSION *

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INTRODUCTION

IN recent years, much has been written concerning a rapidly fatal form of hypertension termed by various observers "malignant hypertension"^{1, 2, 3, 4} "malignant sclerosis"^{5, 6, 7, 8, 9} and "malignant phase of essential hypertension."^{10a} All of these authors have agreed that the elevation of the blood pressure in malignant hypertension is of the essential or primary type. In 1935, however, we¹¹ concluded as a result of the study of a small group of cases, that malignant hypertension is not a disease entity but rather a syndrome in which the hypertension is either primary (essential) or secondary to any one of a number of different diseases. This concept accounted for the differences in the underlying pathologic changes found by earlier authors. It was suggested that the reason certain pathologists believed malignant hypertension to be a specific disease was the fact that they had grouped together pathologically identical cases and found that they presented similar clinical pictures. We felt, on the other hand, that a more accurate characterization of malignant hypertension could be made if all clinically identical cases were included under the diagnosis of malignant hypertension no matter what the pathogenesis might be.

The conclusion that malignant hypertension was merely a syndrome was subsequently stated either expressly or by implication by a number of authors.^{12, 13, 14, 15, 16} Nevertheless, this concept is not generally appreciated. The purpose of this communication is to emphasize our earlier conclusions after a study of a larger series of patients with the syndrome of malignant hypertension coming to autopsy in this hospital. Pertinent case reports in the literature will be analyzed similarly in the light of this concept.

OBSERVATIONS AND DISCUSSION

The clinical manifestations of malignant hypertension have been adequately described by others.² In most of the cases described in the literature and those studied here the malignant phase developed after hypertension had been present in a benign form for some time. In others the hypertension was malignant from the onset. This type of malignant hypertension has been designated the "de novo" form. It is to be noted that the "de novo" form of malignant hypertension may occur in cases of primary hyperten-

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sion^{2, 12, 17} or in patients who for many years have had latent renal disease without hypertension (Case 2).¹⁸ The onset of malignant hypertension is associated with severe headache, visual disturbances, anorexia, vomiting, weight loss and weakness. In addition, there may be impairment of cardiac or renal function. Physical examination reveals severe persistent hypertension and a characteristic retinal picture of edema and hyperemia of the optic discs, sclerosis of the arterioles, retinal hemorrhages and "cotton wool" spots. Examination reveals cardiac enlargement in most instances and signs of impaired renal or cardiac function in many (table 1).

The clinical course is almost always rapidly progressive, terminating fatally. In some instances it is possible to ameliorate or control the signs and symptoms of cardiac or renal failure temporarily but only rarely is the rapid course or the ultimate outcome influenced favorably. In very rare instances, remission of symptoms may occur.^{19, 20} In such cases improvement is heralded by resolution of the retinitis although the blood pressure remains unchanged. Ultimately, i.e., in four to eight years, retinitis recurs and progressive deterioration terminating in death occurs as in other cases of malignant hypertension. Earlier authors^{1, 5, 6, 7, 8, 9, 10a} stressed the invariable terminal occurrence of acute uremia in patients with malignant hypertension. On the other hand, Keith, Wagener, and Kernohan,² and Murphy and Grill³ noted, in addition, failure of other organs, particularly the heart and brain, and recorded the complete absence of renal insufficiency in some instances.

All the patients here studied presented the characteristic clinical findings of malignant hypertension. It is therefore of interest to note the wide variety of pathological lesions found at autopsy in the kidneys and other organs (table 1). It is impossible to conclude that malignant hypertension is a single disease with a uniform pathological picture. Analysis of these and of other reported cases does permit, however, the segregation of instances of malignant hypertension into certain well-defined etiological and pathological groups.

I. Primary or essential hypertension

II. Secondary hypertension

A. Renal disease

1. Glomerulonephritis
2. Pyelonephritis
3. Intercapillary glomerulosclerosis
4. Congenital unilateral hypoplasia
5. Obstruction of renal artery by atherosclerotic plaque
6. Multiple occlusions of small renal arteries
7. Renal infarct
8. Periarteritis nodosa of renal vessels

B. Lead poisoning

TABLE I

Clinical and Postmortem Findings in 15 Cases of Malignant Hypertension

Case No.†	Pa- tient	Sex	Color	Known Duration of Hypertension (Months) Prior to Onset of Malignant Hypertension	Known Duration of Malignant Hyper- tension (Months)	Symptoms† of Malignant Hyper- tension When First Seen	Prog- ress§ to Death	Degree, of Renal Failure Shortly Before Death	Age at Death	Postmortem Findings							Rem
										Weights (in Grams)			Microscopic				
										Heart	Kidneys		Renal Lesions	Vascular Lesions in Other Viscera			
											rt.	lt.		Necrotizing Arteriolitis	Arterio- Medial Hyalinization	Arterio- sclerosis	
1*	I.B.	M.	White	Not known Well until onset	4	C-E	C-R	+++ +	43	650	190	200	Chronic glomeru- lonephritis. Slight arterio- sclerosis. Mini- mal arteriolar hyalinization. Rare necrotiz- ing lesions.	Rare in spleen	Marked in spleen, slight in adrenals and pancreas	Moderate Generalized	Old cor- thromb
2*	E.R.	F.	White	4	6½	E-H-V	Ce-E-W	+	22	240	40	140	Congenital hy- poplasia on right, with mod- erate arterio- sclerosis and arteriolar hya- linization in upper half of right kidney.	Moderate in gall-bladder, few in colon	Moderate in spleen and gall- bladder, slight in pancreas, adrenal and gastrointestinal tract	Slight Patchy	
3*	P.S.	M.	White	Not known Well until onset	6	W-E	Ce	+	56	425	90	130	Marked arterio- sclerosis. Mini- mal arteriolar hyalinization. Occasional nec- rotizing lesions	None	Moderate in spleen. Slight in pancreas and intestine	Moderate Generalized	
4*	S.L.	M.	White	6	8	E-Ce-H	Ce	+	41	400	100	100	Moderate arteriosclerosis, Minimal arteri- olar hyaliniza- tion	None	Moderate in spleen. Slight in pancreas	Moderate Generalized	
5*	F.C.	M.	White	24	6	H-E	Ce-C	+++ +	43	500	100	90	Marked arterio- lar hyalinization with vascular nephritis. Moderate arteriosclerosis. Occasional nec- rotizing lesions	Occasional in prostate, gall- bladder, pan- creas, and retina	Marked in spleen, pros- tate, gall- bladder and retina. Mod- erate in pan- creas and adrenal	Moderate Generalized	

TABLE I (Continued)

6	R.B.	F.	White	4	4		C-E-W	C	0	46	500	160	180	Right renal infarcts. Moderate arteriosclerosis. Slight arteriolar hyalinization	None	Moderate in spleen and pancreas. Slight in heart	Slight in abdominal viscera. Marked in lungs	Mitral stenosis. Thromb in left and right auricles. Pulmonary infarcts
7	J.B.	M.	Negro	Not known Well until onset	4		C-E	C-R	++++	57	690	145	165	Healed glomerulonephritis. Marked arteriosclerosis. Marked arteriolar hyalinization	None	Marked in spleen and pancreas. Slight in liver, testes, and thyroid	Moderate Generalized	
8	W.C.	M.	Negro	Not known Well until onset	3		W-E-V	R	++++	48	650	160	110	Healed glomerulonephritis. Marked arteriolar hyalinization with vascular nephritis. marked arteriosclerosis. Occasional necrotizing lesions	Rare in adrenal	Marked in spleen, pancreas, and adrenal. Slight in bladder and heart	Marked Generalized	
9	A.F.	M.	White	12	3 days		C-E	C	+++	25	640	80	80	Moderate arteriosclerosis. Marked arteriolar hyalinization with vascular nephritis	None	Marked in spleen and adrenal	Slight Generalized including lungs	Course not influenced by splanchicectomy
10	L.H.	F.	White	24	2		E-H-V-C	Ce	+++	47	320	120	180	Left double ureter, with dilatation of the lower, and its pelvis. Chronic glomerulonephritis. Slight arteriolar hyalinization	None	Moderate in spleen and adrenal. Slight in heart, liver, uterus, stomach, and esophagus	Moderate Generalized	Oxycephaly and dwarfism due to theca cell tumor. Diabetes mellitus

* Cases previously reported.¹¹

† All patients showed hypertensive neuroretinopathy and increased spinal fluid pressure.

‡ Symptoms: H—headaches; C—cardiac insufficiency or pain; Ce—hypertensive encephalopathy, psychiatric symptoms or apoplexy; E—impairment of vision, moderate to severe; V—vomiting; W—weight loss, fatigue, weight loss.

§ Progress to death: C—cardiac failure or coronary accident; Ce—hypertensive encephalopathy or apoplexy; R—renal failure, moderate or severe.

|| Degree of renal failure shortly before death: O—normal concentration power; +—loss of concentrating power; ++—loss of concentrating power and reduction of phenolphthalein excretion; +++—slight to moderate blood non-protein nitrogen retention; ++++—severe blood non-protein nitrogen retention.

TABLE 1 (Continued)

Case No.	Patient	Sex	Color	Known Duration of Hypertension (Months) Prior to Onset of Malignant Hypertension	Known Duration of Malignant Hypertension (Months)	Symptoms† of Malignant Hypertension When First Seen	Progress to Death	Degree of Renal Failure Shortly Before Death	Age at Death	Postmortem Findings						Remarks	
										Weights (in Grams)			Microscopic				
										Heart	Kidneys		Renal Lesions	Vascular Lesions in Other Viscera			
											rt.	lt.		Necrotizing Arteriolitis	Arterio- Medial Hyalinization		Arterio- sclerosis
11	L.Q.	F.	White	96	1	V-Ce-C-E	R-C	++++	42	580	140	120	Marked necrotizing arteriolitis. Moderate arteriolar hyalinization. Moderate arteriosclerosis	Occasional in adrenal and pancreas	Moderate in spleen, adrenal and pancreas. Slight in liver	Marked Generalized	
12	W.W.	M.	White	108	12	H-C-E	Ce-C	+	49	830	260		Moderate arteriosclerosis. Slight arteriolar hyalinization. Uric acid crystals in pyramids	None	Moderate in spleen, adrenal, and brain	Moderate Generalized	Gout
13	M.R.	M.	White	24	12	H-E	C	++	36	620	160	160	Marked arteriosclerosis. Minimal arteriolar hyalinization	None	Moderate in pancreas. Slight in heart	Marked in pancreas and gastrointestinal tract. Slight elsewhere	Course influenced by splanchic dorsal sympathectomy
14	H.S.	M.	White	60	3	C-E-W	C-R	++++	40	540	160	120	Marked arteriosclerosis. Slight arteriolar hyalinization. Occasional necrotizing lesions	Occasional in pancreas	Moderate in spleen, pancreas, and adrenal. Slight in heart, gastrointestinal tract, and skeletal muscle	Marked Generalized	
15	H.Y.	M.	White	48	4	C-Ce-W-E	C-Ce-R	++++	45	670	180	180	Aberrant vessel to lower pole of left kidney. Slight healed glomerulonephritis. Marked arteriolar hyalinization with vascular nephritis. Moderate arteriosclerosis. Occasional necrotizing lesions	Occasional in intestine	Marked in spleen, pancreas, and adrenal. Moderate in gall-bladder, gastrointestinal tract, bladder, and skeletal muscle	Moderate Generalized	

C. Endocrine disease

1. Pituitary—basophilic adenoma
2. Adrenal—hypernephroma
paraganglionoma
3. Hyperemesis gravidarum

I. PRIMARY HYPERTENSION

Malignant hypertension heretofore has been considered by most authorities solely as a form of primary hypertension. Fishberg^{10b} considered it the end stage of a previously benign essential hypertension. The concept of "primary" hypertension is difficult to evaluate at the present time. The term "primary" hypertension has in the past been used to designate those instances of hypertension in which no evidence of renal disease is to be found, except for vascular changes considered secondary to hypertension itself. Within recent years, however, it has been shown conclusively that hypertension may develop as a result of impaired renal blood flow without any gross or histological change becoming apparent in the kidneys.²¹ The question naturally arises as to whether patients who show no evidence of primary renal disease might not have had renal ischemia for one reason or another. The great majority of instances of "essential" hypertension reveal at autopsy generalized, including renal, vascular disease (Cases 3, 4, 9, 10, 11, 12, 13, 14). A decision as to whether these renal vascular changes are primary and therefore a cause of hypertension, or secondary and therefore a result of it, usually cannot be made. For the purposes of this discussion "essential" hypertension will be used to include all such cases unless the renal arteriosclerosis exists in the form of one or only a few large, sharply localized occlusive lesions in a renal artery or major branches.

II. SECONDARY HYPERTENSION

A. Renal Disease

1. *Glomerulonephritis.* The present study was initiated seven years ago following the finding at post mortem of chronic glomerulonephritis in a patient with the clinical features of malignant hypertension. Since then, additional cases of this type have been observed (Cases 1, 7, 8, 10, 15). It has been claimed by some authors,^{2, 3} that malignant hypertension with renal failure and chronic glomerulonephritis with uremia may be differentiated by the fact that the latter progresses more slowly and may show remissions in its course. However, cases of acute, subacute, or chronic glomerulonephritis may have an explosive termination in renal failure with severe hypertension, following a period of relative quiescence with "benign" hypertension. It is true that some of these cases of glomerulonephritis may be recognized because of the antecedent history of an acute attack with edema, hematuria, or hypertension, but in many instances of chronic

glomerulonephritis it is not possible to obtain such data. These latter cases of chronic glomerulonephritis with secondary hypertension are indistinguishable clinically from cases of primary malignant hypertension, but are recognized at autopsy. Other authors have made similar observations.^{5, 8, 9, 10c, 13}

2. *Pyelonephritis*. Longcope²² in 1933, reported the case of an eighteen-year-old female with a three months' history of vomiting, headache, clouding of vision, soreness of the back and marked weight loss who showed severe hypertension, enlargement of the heart and malignant neuroretinitis; she died in uremia. Her kidneys showed extreme contraction due to pyelonephritis; no microscopic examination was described. Similar cases have been reported by others.^{15, 23, 24, 25, 26} In a later study of 21 cases of chronic pyelonephritis, Longcope²⁷ described four cases with the syndrome of malignant hypertension. Weiss and Parker¹⁵ have pointed out that the hypertension associated with chronic pyelonephritis is often malignant in type, and that pyelonephritis was responsible for 15 to 20 per cent of the total number of cases of malignant hypertension seen by them. Wagener and Keith²⁸ found a definitely lower incidence of pyelonephritis in this syndrome. No case of pyelonephritis occurred in our group of malignant hypertension. The presence of acute necrotizing arteriolitis in the kidneys has been described in some cases.^{15, 24, 26}

3. *Intercapillary Glomerulosclerosis*. The clinical manifestations of malignant hypertension may appear during the course of the recently described disease known as "intercapillary glomerulosclerosis."^{29, 30} This is a disorder of diabetic patients who present evidences of hypertension and usually the nephrotic syndrome; in occasional instances the symptoms and terminal course may correspond with those of other types of malignant hypertension. Case 2 of the series of Newburger and Peters³⁰ exemplifies this fact.

4. *Congenital Unilateral Hypoplasia of the Kidney*. Ask-Upmark's¹⁸ studies of congenital unilateral renal hypoplasia and developmental anomalies of the kidneys in young females include some instances of the syndrome of malignant hypertension. The fundi revealed "albuminuric retinitis" in three patients who died in uremia. Necrotizing glomerulitis was noted in only one case. Other observers have reported similar cases^{10a, 25, 31} and Case 2 of our own series falls into this group.

5. *Obstruction of Renal Artery by Atherosclerotic Plaque*. Freeman and Hartley³² recorded the findings in a 57-year-old man with the clinical characteristics of malignant hypertension which developed after one kidney was removed because of traumatic laceration. The patient died of cardiac and renal failure and autopsy revealed an atheromatous plaque partially occluding the renal artery of the remaining kidney. Ford and Murphy³³ observed a 33-year-old man with the syndrome of malignant hypertension with normal renal function and urinary findings who died following abdominal sympathectomy. Autopsy revealed widespread arteriolar sclerosis and partial occlusion of the left renal artery by a large arteriosclerotic plaque.

6. *Multiple Occlusions of Small Renal Arteries.* That occlusion of smaller arteries also may give rise to the syndrome of malignant hypertension is suggested by the case reported by Leiter.³⁴ The patient was a 40-year-old man who developed severe progressive hypertension with the manifestations of malignant hypertension and died of heart failure without significant impairment of renal function. Autopsy revealed occlusion of the small renal arteries of unknown origin.

7. *Renal Infarct.* The case of Boyd and Lewis³⁵ was that of a 31-year-old man with the clinical features of malignant hypertension who was relieved of these manifestations for four years after the removal of a kidney which was the site of arterial narrowing and extensive infarction. Case 6 of our series also had renal infarcts.

8. *Periarteritis Nodosa of Renal Arteries.* Friedberg and Gross'³⁶ series of cases of rheumatic heart disease with periarteritis nodosa includes one instance (Case 4) with history and physical findings typical of malignant hypertension. Reports of other instances of malignant hypertension associated with periarteritis nodosa with or without rheumatic heart disease are available in the literature.³⁷ Kimmelstiel and Wilson¹³ have shown a close correlation between the occurrence of hypertension and renal vascular lesions in periarteritis nodosa.

B. Lead Poisoning

Certain cases of chronic lead poisoning with severe hypertension may exhibit convulsive seizures or other acute cerebral manifestations. Such patients may present the typical neuroretinopathy of malignant hypertension.³⁸

C. Endocrine Disease

1. *Pituitary Basophilism.* Cases of pituitary basophilism may present the syndrome of malignant hypertension.^{4, 10e, 39, 40} Death may be due to failure of the heart, kidneys, or brain. It is of interest that necrotizing arteriolitis of the kidneys has been found in some cases.⁴⁰

2. *Adrenal Glandular Tumors.* Oppenheimer and Fishberg⁴¹ in 1924 described a patient who presented a short history of severe hypertension, physical findings of severe diastolic hypertension, malignant neuroretinitis and cardiac hypertrophy, and a course terminating in death from cardiac insufficiency. Autopsy revealed hypernephroma of the right suprarenal gland, multiple adenomata of the left suprarenal gland and normal kidneys. Winkel's⁴² case also falls into this category.

Palmer and Castleman⁴³ recently observed a case of paraganglionoma of the adrenal gland in a 23-year-old female with the syndrome of malignant hypertension. The patient died during an attack of paroxysmal hypertension. At autopsy, the heart weighed 250 grams and the kidneys were normal. A similar case was a 14-year-old girl who died of acute heart failure and cerebral accident described by Kremer.⁴⁴ The kidneys revealed

recent anemic infarcts, arteriolar and intraglomerular hyalin thrombosis and mild eccentric thickening of the intima of the renal arteries.

3. *Hyperemesis Gravidarum*. Hyperemesis gravidarum, a syndrome as yet incompletely understood, presents striking similarities to malignant hypertension according to Klemperer and Otani.⁸ It is here included under the heading of endocrine disorders although it is not conclusively proved that this is the nature of the disease.

It is clear from all of the above discussion that malignant hypertension is a syndrome which may occur in "primary" or any of the varieties of "secondary" hypertension. The considerations outlined above substantiate our earlier conclusions¹¹ and corroborate those of other observers.^{12, 13, 14, 15, 16}

The concept that malignant hypertension is a syndrome which may occur in patients with either primary or secondary hypertension explains the wide variety of pathological lesions found in the kidneys of such patients post mortem. The histologic changes of the kidney vary, depending upon the duration of the elevation of the blood pressure and with the nature of the underlying morbid process. In some instances, the kidneys are not strikingly abnormal (Case 2).

Some authors^{1, 5, 6, 8, 10f} consider the essential pathologic change in malignant hypertension to be productive endarteritis and necrotizing renal arteriolitis. The latter finding is felt to be of greater diagnostic value since the former may occasionally be absent. These "specific" changes are encountered often, however, in other conditions. Necrotizing arteriolitis also has been found frequently in the kidneys of patients with hypertension secondary to various forms of renal pathology such as diffuse glomerulonephritis^{10g, 13} and pyelonephritis.^{15, 24, 26} Such patients may or may not present the typical syndrome of malignant hypertension. On the other hand it has been shown repeatedly^{2, 3, 23} that the kidneys of patients with the syndrome of malignant hypertension may contain no such lesions (Cases 2, 4, 6, 7, 9, 10, 12, 13) or an extremely small number³ (Cases 1, 3, 5, 8, 14, 15). In our own series of nine patients with marked renal insufficiency, one had many necrotizing renal arteriolar lesions, five had few, and three had none. In some instances foci of acute necrotizing arteriolitis may be more numerous in viscera other than the kidneys (Case 2); such foci may also be numerous in other viscera when the kidneys show many such lesions (Case 11). Renal necrotizing arteriolitis therefore cannot be considered specific for any single morbid process. Its presence in the kidneys or elsewhere may, however, indicate an unusually severe degree or prolonged duration of hypertension. Certain experimental studies in animals afford confirmatory evidence in this regard.^{16, 45, 46}

Renal insufficiency was formerly held to be an invariable concomitant of necrotizing arteriolitis in the kidneys; although this is no longer believed by some authors, many still hold to this concept. Murphy and Grill³ and Klemperer and Otani⁸ described necrotizing arteriolitis in the kidneys of

patients in whom there was not the slightest sign of renal insufficiency and Fishberg stated that, "In the malignant phase of essential hypertension, necrosis of the renal arterioles may occur before there is any significant renal insufficiency."^{10h} On the other hand, Murphy and Grill,³ Cain,²³ and Keith, Wagener, and Kernohan² failed to observe renal arteriolar necrosis in a number of instances in which death definitely was due to uremia.

The mechanism by which the benign course of primary or secondary hypertension is suddenly and dramatically transformed into the rapid, progressive, downhill course of the syndrome of malignant hypertension is not understood. Attempts to incriminate infections, toxins, mental stress, or other factors have been inconclusive.

The clinical course of the syndrome of malignant hypertension is not significantly influenced by the underlying pathologic process responsible for its appearance. In all but rare cases the prognosis is poor unless the syndrome develops following renal infarction³⁵ or in association with adrenal tumors.⁴³ Surgery in these instances may offer a means of altering an otherwise hopeless course. Available evidence indicates that progression or regression of retinal changes are the best guides as to the subsequent clinical course.^{19, 20} Sympathetic surgery in patients with malignant hypertension has been uniformly disappointing.⁴⁷ The need is clear, therefore, for extremely thorough and meticulous search for evidence of renal infarction or adrenal tumor, since thus far these are the only conditions giving rise to malignant hypertension in which improvement may be expected.

SUMMARY AND CONCLUSIONS

1. Malignant hypertension is a syndrome which may occur
 - a. With no evidence of previously existing hypertension,
 - b. As the end stage of essential hypertension, with or without uremia,
 - c. As the end stage of a miscellaneous group of conditions characterized by secondary hypertension.
2. It is usually impossible to decide during the life of a patient exhibiting the syndrome of malignant hypertension whether the hypertension is primary, or secondary to some unrecognized morbid process.
3. Since malignant hypertension is a syndrome and not a specific disease, the renal pathological findings will show wide variation from patient to patient. The presence of acute necrotizing arteriolitis does not establish the diagnosis of primary malignant hypertension nor does its absence rule it out.
4. Whatever the nature of the underlying pathological process responsible for the appearance of the syndrome of malignant hypertension, the prognosis is almost always poor. Exceptions are apparently to be found in those rare surgically amenable instances in which the syndrome is precipitated by renal infarction or the development of certain tumors of the adrenal glands.

5. In rare cases of apparently typical malignant hypertension remission of symptoms and resolution of the retinitis may occur; the blood pressure, however, remains unchanged. After a period of four to eight years, the downhill course again becomes manifest with fatal termination as in other cases of malignant hypertension.

REFERENCES

1. VOLHARD, F., and FAHR, T.: Die Brightsche Nierenkrankheit, Klinik, Pathologie und Atlas, 1914, Julius Springer, Berlin.
2. KEITH, N. M., WAGENER, H. P., and KERNOHAN, J. W.: Syndrome of malignant hypertension, Arch. Int. Med., 1928, xli, 141.
3. MURPHY, F. D., and GRILL, J.: So-called malignant hypertension; clinical and morphological study, Arch. Int. Med., 1930, xlv, 75.
4. ELLIS, A.: Malignant hypertension, Lancet, 1938, i, 977.
5. FAHR, T.: Über Nephrosklerose, Virchow's Arch. f. path. Anat., 1919, ccxxvi, 119. Henke und Lubarsch's Hand. d. path. Anat. u. Hist., Berlin, 1925, vii, 405. Maligne Nephrosklerose, in Die Pathologische Anatomie des Morbus Brightii, 1934, Julius Springer, Berlin, p. 934.
6. STERN, M.: Über einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem makroskopischen Bilde der "grossen bunten Niere," Virchow's Arch. f. path. Anat., 1924, ccli, 718.
7. HERXHEIMER, G.: Über Arteriolonekrose der Nieren, Virchow's Arch. f. path. Anat., 1924, ccli, 709.
8. KLEMPERER, P., and OTANI, S.: Malignant nephrosclerosis (Fahr), Arch. Path., 1931, xi, 60.
9. MACMAHON, H. E., and PRATT, J. H.: Malignant nephrosclerosis (malignant hypertension), Am. Jr. Med. Sci., 1935, cclxxxix, 221.
10. (a) FISHBERG, A. M.: Hypertension and nephritis, ed. 4, 1939, Lea and Febiger, Philadelphia, p. 674. (b) *ibid.*, p. 681. (c) *ibid.*, p. 508. (d) *ibid.*, p. 264. (e) *ibid.*, p. 683. (f) *ibid.*, p. 677. (g) *ibid.*, p. 506. (h) *ibid.*, p. 678.
11. DEROW, H. A., and ALTSCHULE, M. D.: Malignant hypertension, New England Jr. Med., 1935, ccxiii, 951.
12. PAGE, I. H.: A clinical study of malignant hypertension, ANN. INT. MED., 1939, xii, 978.
13. KIMMELSTIEL, P., and WILSON, C.: Benign and malignant hypertension and nephrosclerosis, Am. Jr. Path., 1936, xii, 45.
14. WILLIAMS, J. R., JR., and HARRISON, T. R.: Clinical pictures associated with increased blood pressure: a study of 100 patients, ANN. INT. MED., 1939, xiii, 650.
15. WEISS, S., and PARKER, F., JR.: Pyelonephritis: its relation to vascular lesions and to arterial hypertension, Medicine, 1939, xviii, 221.
16. WILSON, C., and BYROM, F. B.: Renal changes in malignant hypertension, experimental evidence, Lancet, 1939, i, 136.
17. SUTER, F.: Nieren und ableitende Harnwege, in VOLHARD, F.: Handb. inn. Med., 1931, Julius Springer, Berlin, vol. 6, part 2, p. 1693.
18. ASK-UPMARK, E.: Über juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung, Acta. Path. et Microbiol. Scandinav., 1929, vi, 383.
19. OPPENHEIMER, B. S., and FISHBERG, A. M.: Hypertensive encephalopathy, Arch. Int. Med., 1928, xli, 264.
FISHBERG, A. M.: Personal communication to the authors.
20. KEITH, N. M., and WAGENER, H. P.: Acute vasospastic hypertension, a case with signs of cerebral irritation and severe retinitis with remission, Am. Jr. Med. Sci., 1935, cxc, 45.

- KEITH, N. M.: Personal communication to the authors.
21. GOLDBLATT, H.: Experimental hypertension induced by renal ischemia, Harvey Lectures, 1937-38, The Williams and Wilkins Company, Baltimore, p. 237.
 22. LONGCOPE, W. T., and WINKENWERDER, W. L.: Clinical features of contracted kidney due to pyelonephritis, Bull. Johns Hopkins Hosp., 1933, liii, 255.
 23. CAIN, E. F.: Malignant hypertension: the histologic changes in kidneys, Arch. Int. Med., 1934, liii, 832.
 24. MALLORY, T. B.: Pyelonephritis and hypertension, Cabot Case 18032, New England Jr. Med., 1932, ccvi, 129.
 25. FAHR, T.: Über pyelonephritische Schrumpfnieren und hypogenetische Nephritis, Virchow's Arch. f. path. Anat., 1938, cccii, 140.
 26. KIMMELSTIEL, P., and WILSON, C.: Inflammatory lesions in the glomeruli in pyelonephritis in relation to hypertension and renal insufficiency, Am. Jr. Path., 1936, xii, 99.
 27. LONGCOPE, W. T.: Chronic bilateral pyelonephritis: its origin and its association with hypertension, ANN. INT. MED., 1937, xi, 149.
 28. WAGENER, H. P., and KEITH, N. M.: Diffuse arteriolar disease with hypertension and the associated retinal lesions, Medicine, 1939, xviii, 317.
 29. KIMMELSTIEL, P., and WILSON, C.: Intercapillary lesions in the glomeruli of the kidney, Am. Jr. Path., 1936, xii, 83.
 - DEROW, H. A., ALTSCHULE, M. D., and SCHLESINGER, M. J.: The syndrome of diabetes mellitus, hypertension and nephrosis, New England Jr. Med., 1939, ccxxi, 1012.
 30. NEWBURGER, R. A., and PETERS, J. P.: Intercapillary glomerulosclerosis: a syndrome of diabetes, hypertension, and albuminuria, Arch. Int. Med., 1939, lxiv, 1252.
 31. SCHWARZ, H.: Kidney disease in infants and children. II. Malignant hypertension nephritis. Primary sclerotic kidney, Am. Jr. Dis. Child., 1934, xxvii, 233.
 32. FREEMAN, G., and HARTLEY, G., JR.: Hypertension in a patient with a solitary ischemic kidney, Jr. Am. Med. Assoc., 1938, cxi, 1159.
 33. FORD, F. R., and MURPHY, E. L.: Increased intracranial pressure, a clinical analysis of the causes and characteristics of several types, Bull. Johns Hopkins Hosp., 1939, lxiv, 369.
 34. LEITER, L.: Unusual hypertensive renal disease, Jr. Am. Med. Assoc., 1938, cxi, 507.
 35. BOYD, C. H., and LEWIS, L. G.: Nephrectomy for arterial hypertension, Jr. Urol., 1938, xxxix, 627.
 - BOYD, C. H.: Personal communication to the authors.
 - HARRIS, S., JR.: Personal communication to the authors.
 36. FRIEDBERG, C. K., and GROSS, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, with note on abdominal rheumatism, Arch. Int. Med., 1934, liv, 170.
 37. BENNETT, G. A., and LEVINE, S. A.: Two cases of periarteritis nodosa; one with unusual manifestations (meningeal form), Am. Jr. Med. Sci., 1929, clxxvii, 853.
 - DERICK, C. L., and HAAS, G. M.: Diffuse arteritis of syphilitic origin, Am. Jr. Path., 1935, xi, 291.
 - WEVER, G. K., and PERRY, I. H.: Periarteritis nodosa: report of case with fatal perirenal hemorrhage, Jr. Am. Med. Assoc., 1935, civ, 1390.
 38. OLIVER, T.: In ALLBUTT and ROLLESTON, System of Medicine, 1912, The Macmillan Company, New York, Vol. 2, p. 1052.
 - SCHROEDER, H. A., and STEELE, J. M.: Studies on "essential hypertension." I. Classification, Arch. Int. Med., 1939, lxiv, 927.
 39. MACMAHON, H. E., CLOSE, H. G., and HAAS, G.: Cardiovascular renal changes associated with basophil adenoma of anterior lobe of pituitary (Cushing's syndrome), Am. Jr. Path., 1934, x, 177.
 - RUSSELL, D. S., EVANS, H., and CROOKE, A. C.: Two cases of basophil adenoma of the pituitary gland, Lancet, 1934, ii, 240.

- CLOSE, H. G.: Basophil adenoma of the pituitary gland with renal changes, *Brit. Med. Jr.*, 1935, i, 356.
40. GOULEY, B. A.: Basophilic adenoma of the pituitary: report of a case of "pituitary hypertension," terminating in cerebral apoplexy, *ANN. INT. MED.*, 1935, viii, 1294.
41. OPPENHEIMER, B. S., and FISHBERG, A. M.: Association of hypertension with suprarenal tumors, *Arch. Int. Med.*, 1924, xxxiv, 631.
42. WINKEL, M.: Virilismus Suprarenalis bei einem Adenom der Nebennierenrinde, *Deutsch. Arch. f. klin. Med.*, 1928, clix, 1.
43. PALMER, R. S., and CASTLEMAN, B.: Paraganglioma (chromaffinoma, pheochromocytoma) of the adrenal gland simulating malignant hypertension, *New England Jr. Med.*, 1938, ccxix, 793.
44. KREMER, D. N.: Medullary tumor of the adrenal glands with hypertension and juvenile arteriosclerosis, *Arch. Int. Med.*, 1936, lvii, 999.
45. GOLDBLATT, H.: Studies on experimental hypertension. VII. The production of the malignant phase of hypertension, *Jr. Exper. Med.*, 1938, lxxvii, 809.
46. WILSON, C., and PICKERING, G. W.: Acute arterial lesions in rabbits with experimental renal hypertension, *Clin. Sci.*, 1938, iii, 343.
47. PAGE, I. H.: Medical aspects of surgical treatment of hypertension, *Jr. Am. Med. Assoc.*, 1938, cx, 1161.

HEPATO-LENTICULAR DEGENERATION (WILSON'S DISEASE) FOLLOWING SPLENECTOMY; INTER-RELATIONSHIP OF THE RETICULO-ENDOTHELIAL AND CENTRAL NERVOUS SYSTEMS *

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IN two instances we have observed following splenectomy the rapid onset of symptoms indicating hepatolenticular degeneration. In both cases the operation had been performed because of anemia and purpura associated with splenomegaly. So far as we can determine, the development of the hepatolenticular syndrome has not hitherto been reported as a sequel in the clinical course of any cases of purpura in which splenectomy has been done. These cases therefore are being presented to record this occurrence, to direct attention to a possible contra-indication for splenectomy, and as a basis for discussion of the inter-relationship that we feel exists between the reticulo-endothelial system and the central nervous system.

CASE REPORTS

Case 1. Mild Parkinsonian tremors for four years following a febrile illness diagnosed as typhoid fever. Hemorrhagic diathesis and enlarged spleen. Splenectomy. Rapid increase in tremors with extreme muscle rigidity, and development of Kayser-Fleischer ring.

N. G., a 23 year old unmarried typist, was admitted to the Israel Zion Hospital, Brooklyn, August 20, 1932. For one week she had been aware that her abdomen was swollen. She gave a history of several upper respiratory infections, and had had an illness four years prior to admission which had been diagnosed as typhoid fever. A tremor of the upper extremities which had been present for four years was regarded as caused by chronic encephalitis with mild Parkinsonism. There was also a history of menstrual irregularity, bleedings from the gums and a tendency to bleed excessively from slight wounds. The history otherwise was irrelevant. A sister of the patient, with a history of epistaxis, had been examined and her spleen found to be enlarged. On examination the patient exhibited a coarse tremor of the extremities which increased with voluntary movement. The spleen was enlarged and was felt two fingers' breadth below the level of the umbilicus. Blood examination revealed leukopenia, a low platelet count and was suggestive of splenic anemia. The icteric index was 35; urea N was 19 mg. per cent; glucose, 80 mg. per cent; cholesterol, 154 mg. per cent. The urine was negative for urobilin and urobilinogen. The Wassermann reaction in the blood and spinal fluid was negative.

The history of typhoid fever offered a possible clue to the etiology of the enlarged spleen. The atypical clinical picture gave rise to conflicting diagnoses. However, on the day following admission, one of the writers (H. J.) offered the opinion

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that "in the presence of a large spleen and the tremor, Wilson's disease must be considered."

On September 10, 1932 splenectomy was performed by Dr. Wolfson. The spleen was enlarged to about four times the normal size. The liver was found to be contracted and markedly cirrhotic with large hobnail nodules throughout the surface. Pathologic examination of the spleen revealed diffuse hyperplasia of the reticulum, hyperplasia of the sinuses, and atrophy of the follicles.

The post-operative reaction was good. On the thirteenth day later, it was noted that though the patient was comfortable, the tremor had increased. On that date, one of the writers, (A. M. R.), examined her for the first time and noted that "she presented fixed facies, rigidity of all the muscles, with a coarse rhythmic tremor of the hands, and bilateral Babinski signs. There is brownish-green pigmentation on the margins of the cornea. The association of a cirrhotic liver, the basal ganglia syndrome, and the circumcorneal pigmentation suggests the diagnosis of hepatolenticular disease."

From that time she became steadily more rigid and tremulous. On November 8 it was noted that she presented marked inversion of the right foot with both phasic and kinetic Babinski signs. Pigmentation of the corneal margins had increased. The neurological picture developed with rapid strides. Disorder of speech and swallowing ensued along with emotional instability. Within three months following the operation she was so rigid and helpless that she could no longer feed herself or talk. December 8 she was transferred to the Kings County Hospital and died there eight days later of broncho-pneumonia. Autopsy was not performed.

Discussion: The tremors which this patient manifested on admission were most likely due to striatal disease dating back to the febrile illness which occurred four years prior to admission and which had been diagnosed, perhaps erroneously, as typhoid fever. This tremor, rightly termed Parkinsonian, had been associated with no gross disability. Following the splenectomy, however, the tremor rapidly became extreme along with the muscular rigidity, and the Kayser-Fleischer ring was noticed for the first time. The neurological disorder then progressed rapidly. The splenectomy undoubtedly played an important rôle in the aggravation of the striatal disease.

Case 2. Prolonged chronic hemorrhagic diathesis for many years. Doubtful symptoms suggesting encephalitis epidemica. Splenectomy followed by development of tremors, Kayser-Fleischer ring, and the clinical picture of hepatolenticular disease.

R. B., a 25 year old, unmarried, female factory worker was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, November 2, 1934. Since the age of eleven she had complained of lumbar pains and was subject to frequent nose bleeds. As long as she could recall, the slightest bruises caused ecchymotic areas. She had had excessive bleeding after tooth extractions.

In January 1933, she developed frontal headaches associated with spots before the eyes. About the same time she began to tire easily, she slowed up in her work and lost her job on this account. Several months later she was observed at Bellevue Hospital. Examination there revealed marked anemia (hemoglobin 35 per cent), enlargement of the spleen down to the umbilicus, and an enlarged liver. The diagnosis of Banti's syndrome was made at Mt. Sinai Hospital, and on November 6, 1933, splenectomy was performed. She had a severe postoperative reaction with tachycardia and fever. It is interesting that several days after the operation she was examined by a neurologist who found ulnar neuritis in the left hand attributed to pressure during anesthesia. Apparently he noted no signs of any extrapyramidal disorder. At operation it was

found that the liver was markedly contracted and had a hobnail appearance. The spleen was enlarged and weighed 975 grams. Its cut surface showed ring hemorrhages, and microscopically there was "diffuse sinus hyperplasia, reticular hyperplasia with annular perifollicular hemorrhage."

Prior to operation, the blood examination had shown: hemoglobin 63 per cent, red blood cells 4,320,000, white blood cells 4,100, polymorphonuclear leukocytes 78 per cent, lymphocytes 20 per cent, eosinophiles 1 per cent, monocytes 1 per cent and platelets 70,000. The bleeding time was 10 minutes, clotting time, 2 minutes, and the tourniquet test was normal. Sternal biopsy was negative. December 5, 1933, one month after operation, the examination showed: hemoglobin 81 per cent, red blood cells 4,500,000, white blood cells 7,500, polymorphonuclear leukocytes 58 per cent, lymphocytes 29 per cent, monocytes 13 per cent, and platelets 470,000.

She was examined again three months later, at which time she complained of tremors of both hands of three weeks' duration, and also that her legs felt rigid. February 23, slit lamp study demonstrated the Kayser-Fleischer ring. Following that she was observed on two occasions at Mt. Sinai Hospital, the last time in July, 1934, for hematuria which was regarded as part of the hemorrhagic diathesis.

On admission to the Jewish Sanitarium and Hospital for Chronic Diseases, the tremors in the upper limbs, first noted two months after the operation, had become intensified. She presented a tendency to fixity of facial expression. She smiled readily and was often facetious. In repose, with the limbs relaxed, there were no extraneous movements. While performing the finger to nose test, movements were smoothly performed until the finger reached its goal. Tremor then developed, at first mild, then increasing in amplitude to become a wild, rhythmic, beating movement which persisted until the effort ceased. This tremor differed from the usual intention tremor in that it did not appear during the phase of activity but began when the act was completed. There was marked hypertonia in the limbs. There was loss of associated arm swing on the right side during walking and the right upper limb was tremulous and hung limply at the side. The outstretched arm showed a rhythmic tremor first in the hand which increased in amplitude and rate to involve finally the entire limb. It resembled the beating movements of a bird's wings in flying. There was a fine tremor of the head noted especially while walking. Her speech had a nasal quality and was somewhat syllabic. A circumcorneal ring of greenish pigmentation was noted in both eyes. Neurologic examination otherwise was negative.

Discussion: The hemorrhagic diathesis had undoubtedly existed for many years. The headaches, blurred vision, and slowing up of activities which developed in January 1933, suggested that these symptoms were due to epidemic encephalitis. However, she presented none of the objective symptoms of disease of the basal ganglia until two months after the operation, when the entire neurologic syndrome was initiated and progressed rapidly until there was no doubt that the clinical disorder fitted into the group of hepato-lenticular disease.

Subsequently her course remained stationary for a time. August 2, 1935, in a fit of despondency, she committed suicide by jumping from a window. She died immediately.

Autopsy. There was a depressed fracture of the skull involving the entire right frontal and parietal areas, the bone being driven into the brain and crushing it. There was a moderate subdural hemorrhage over the left parietal region. The liver weighed 1800 grams. It was greenish brown in color, its surface divided into nodules of approximately equal size and having an average diameter of 15 mm. The nodules

projected above the surface and were marked off by depressed grayish white fibrous zones. The cut surface of the liver had throughout the same nodular structure as was seen on the surface. The normal anatomic relationship of the vessels was preserved. No gross regenerating nodules were seen. There were no changes in the portal radicles.

On microscopic examination of the liver, Glisson's capsule was thickened. The parenchyma was divided into nodules by fibrous tissue formed in the portal spaces and

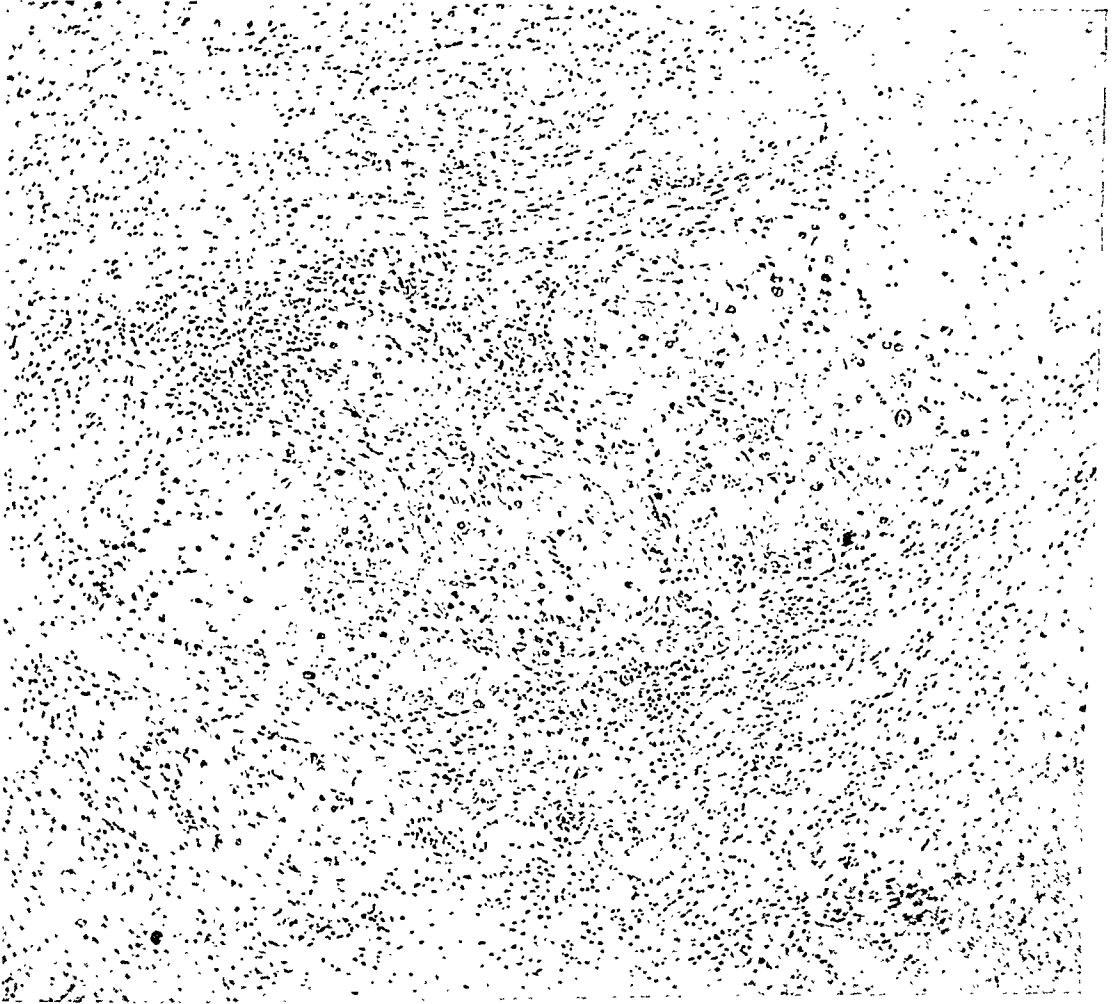


FIG. 1. Section of liver. (Low power.) Note degeneration of liver lobule and increase in fibrous tissue in and cellular infiltration of portal spaces. H. and E.

extending as fine fibrils into the peripheral portions of the nodules and isolating at times small groups of liver cells (figure 1). The nodules varied slightly in size. The normal relationship of the structures of the liver lobule to one another was not disturbed. There were moderate numbers of new-formed biliary radicles of not very recent origin. The parenchymal picture was one of swelling of all the polygonal cells to the extent that all sinusoids were compressed and only an occasional erythrocyte was present in them. The individual cells as a whole were well defined, with a clear, finely granular, vacuolated cytoplasm. The nuclei were also well preserved. There were, however, groups of cells which had undergone various degrees of degeneration.

up to complete atrophy. These groups varied in location but were chiefly near the periphery of the lobules and occasionally also close to the central veins. These cells lacked recognizable cytoplasm, the nuclei were in various stages of disintegration, and in some areas the picture approached that of acute yellow atrophy. Cellular infiltration in the form of moderate numbers of lymphocytes and occasional plasma cells was present in the portal fibrous tissue and also in small groups in the atrophic areas of parenchyma. Small collections of bile pigment were present in and around the degenerating cells. Küpfer cells were not increased in number though they appeared relatively prominent because of the lack of other sinusoid elements.

The pathologic diagnoses were:

1. (a) Cirrhosis of liver, peri- and intralobular, degenerative type.
(b) Fibrosis of liver capsule.
2. Fractured skull, depressed, of right frontal and parietal bones and base of skull, traumatic (suicidal), with: (a) laceration of dura and brain, (b) subdural hemorrhages, direct and contre-coup.
3. Acute focal non-suppurative myocarditis, non-specific, with: (a) focal myocardial degeneration, (b) focal myocardial fibrosis.

Gross Findings in the Brain: The brain was rather small, weighing approximately 960 gm. in the fixed state. Over the convexities were scattered slight extravasations of blood. These were also present over the left cerebellar hemisphere. The surface of the brain was normal. There was no deepening nor widening of the sulci. On cross section the caudate nuclei were flattened and the lenticular nuclei seemed somewhat shrunken. In the posterior segments of the basal ganglia in the right hemisphere there were gross degeneration and disintegration of the basal portions. This region seemed especially friable and was easily broken in handling.

Microscopic Findings: There were diffuse, scattered ganglion cell changes in the cerebral cortex throughout all lobes with frequent diffuse and focal dropping out of cells (figure 2). Many ganglion cells showed various stages of chronic cell disease consisting of both sclerosis and ischemic homogenous degeneration, and numerous cell shadows were observed. The changes were most marked in the deeper layers of the cortex where there was considerable proliferation of oligodendroglia. There was a moderate degree of vascular change throughout the hemispheres with moderate vascular proliferation and occasional small perivascular necroses. An early status spongiosus was observed occasionally in the white matter adjacent to the cerebral cortex. There was a large increase in oligodendroglia undergoing acute swelling throughout the white matter of the cerebral hemispheres. Small amounts of perivascular metachromatic pigment granules were frequently encountered throughout the hemispheres in the regions showing ganglion cell destruction. Perivascular infiltrates of lymphocytes and gitter cells were frequently encountered but were usually small. The most marked changes were observed in the basal ganglia. Caudate and lenticular nuclei were considerably shrunken, especially in the posterior segments. Anteriorly, the basal ganglia showed some loss of cells and various stages of degeneration in all the remaining cells. Posteriorly, all the ganglion cells of the globus pallidus and putamen had completely disappeared (figure 3). Here there was but little glial proliferation as compared with other regions, despite the more advanced cell changes. This suggested that the process was much older here and had become somewhat stationary. The caudate nucleus showed considerable glial proliferation but no fiber formation.

The hypothalamus showed an early spongy state of a fine-meshed character which extended into the ventral thalamus. A similar spongy state of more grossly meshed character involved the caudate and lenticular nuclei. In the preparation of the tissue the lenticular nucleus was found to be unusually friable. The hypothalamic regions



Fig. 2. Frontal cortex (medium power). Acellular areas at "a." Thionin stain.

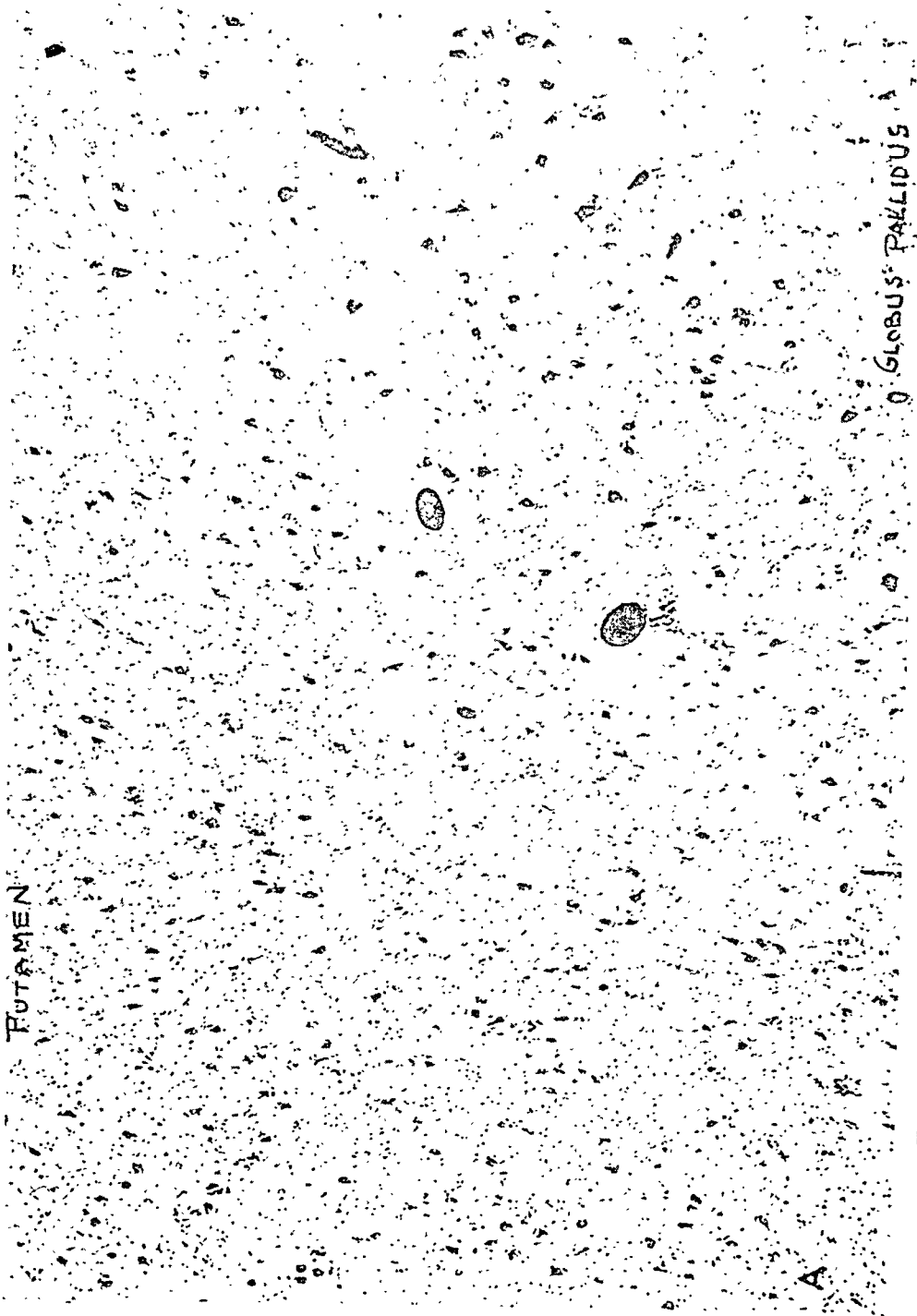
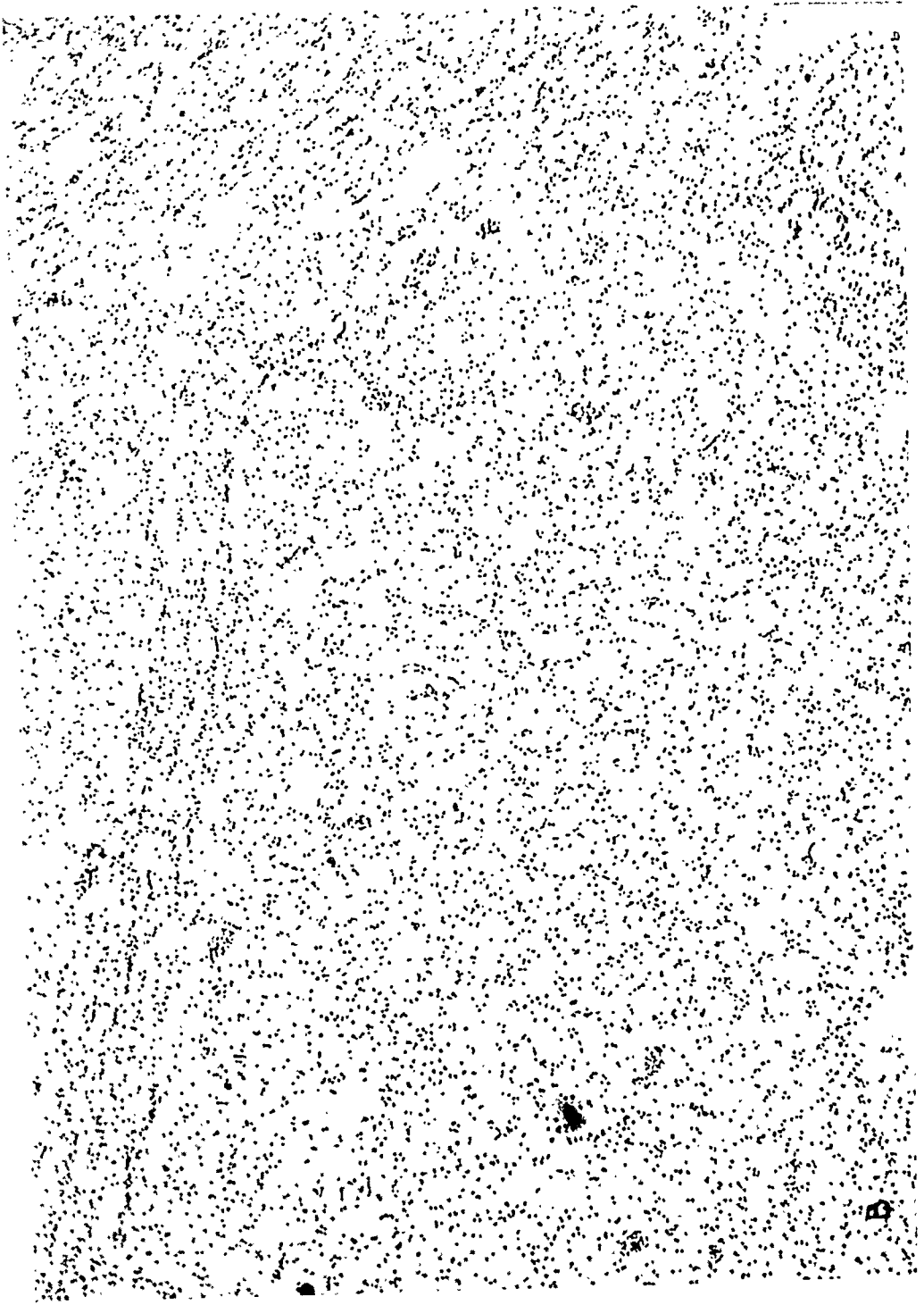


FIG. 3. The lenticular nucleus showing adjacent portions of putamen and globus pallidus. Thionin stain. (Low power.) (A). Normal control.



(B). Present case, corresponding region. Note disappearance of ganglion cells and considerable gliosis.

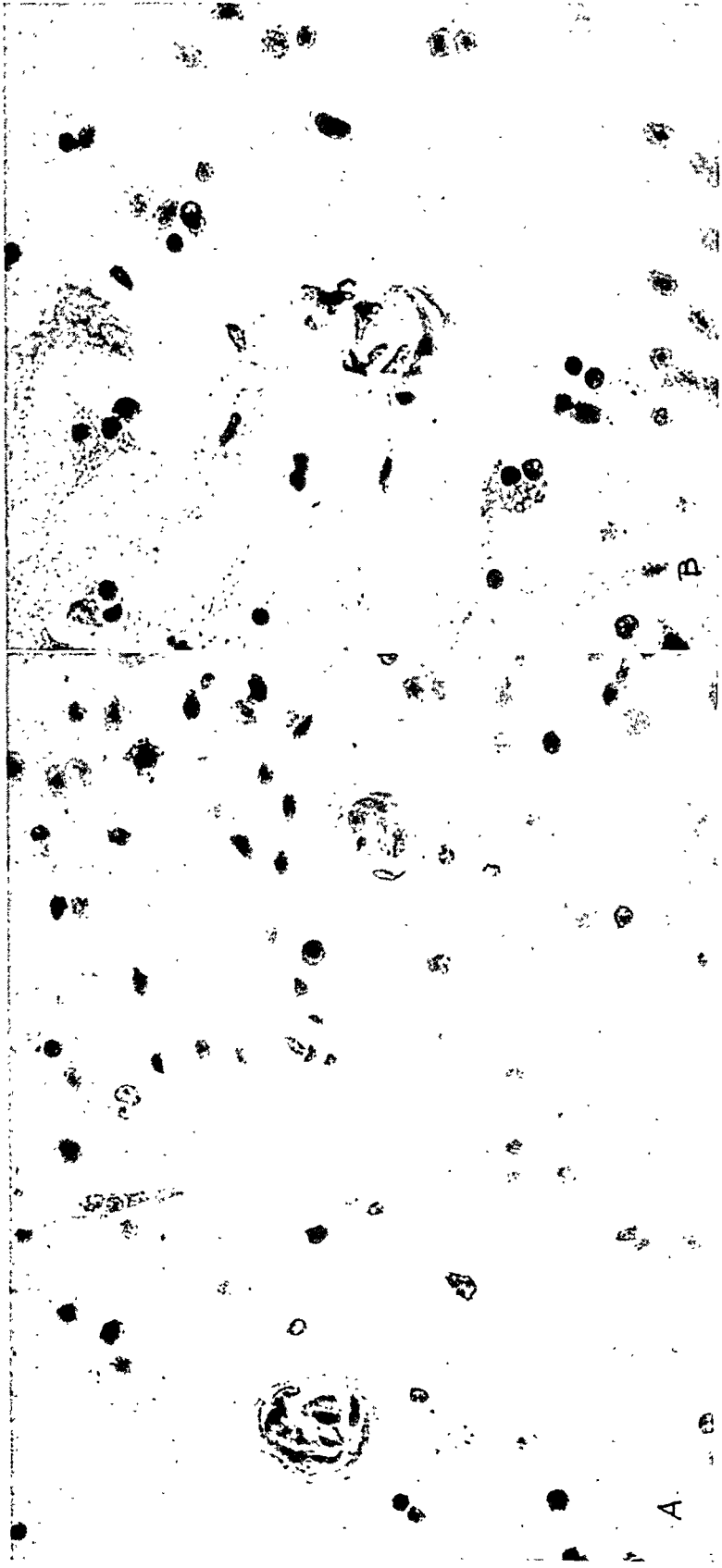


FIG. 4. Thionin stain. (High power.)
(A). Typical vascular endothelial proliferation in cortex.
(B). Perivascular spongy state.

and the ventral and lateral thalamic nuclei showed considerable ganglion cell change, largely of a chronic ischemic homogeneous type, with frequent cell shadows and considerable loss of cells. Mild ganglion cell changes were noted in the remainder of the thalamus but little cell loss. There was a moderate degree of ganglion cell change in the substantia nigra with some cell shadows. Mild but diffuse ischemic changes were seen in many of the cells of Ammon's horn with some cell loss.

Vascular changes, consisting predominantly of endothelial proliferation and thickening, were observed in the region of the basal ganglia, being most marked in the substantia nigra and the hypothalamus but also marked in the lenticular and caudate nuclei. Similar changes of a milder degree and involving small vessels especially

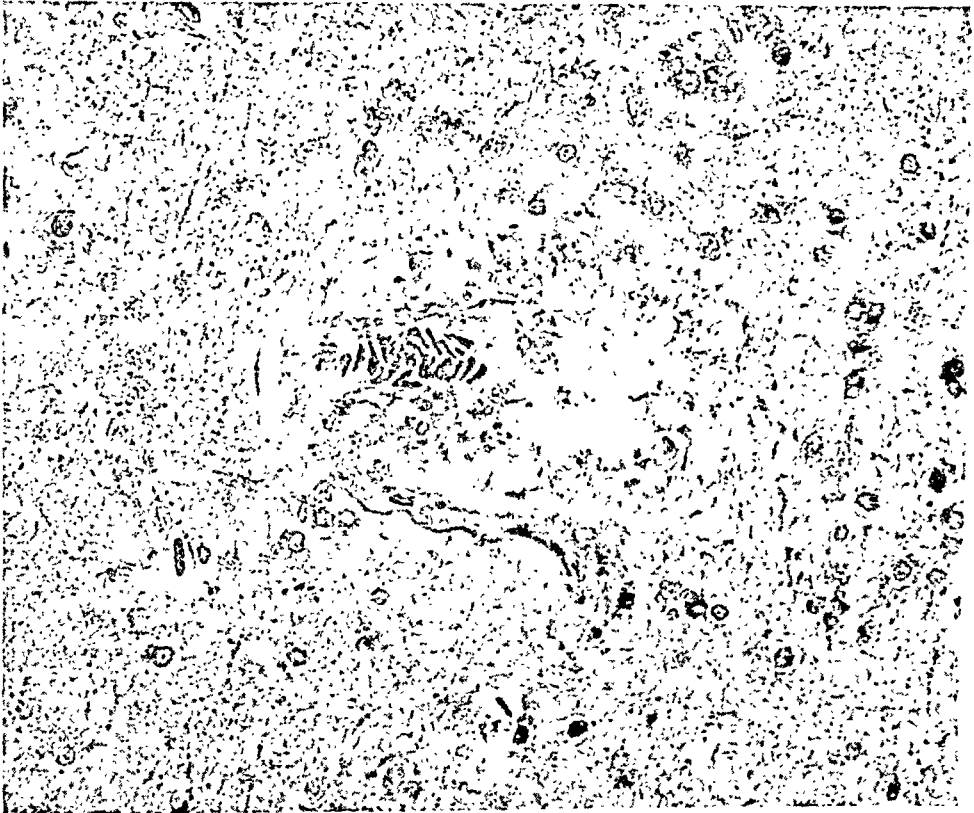


FIG. 5. Perivascular spongy necrosis from frontal cortex. Hortega silver impregnation. Compare with figure 4, B. (High power.)

were noted frequently in the cortex (figures 4 and 5). Frequent moderate perivascular infiltration with lymphocytes and gitter cells was noted in the substantia nigra and hypothalamus. Perivascular accumulation of degenerative pigment in small amounts was frequent in the lenticular nucleus and to a lesser degree in the hypothalamus and the substantia nigra. In the caudate nucleus, particularly with the silver and gold stains, a slight perivascular spongy state was observed about all vessels, large and small, with precipitates of granular, amorphous material taking up the silver and gold (figure 6).

Glial proliferation was marked throughout the region of the diencephalon. This was predominantly astrocytic and the changes were both progressive and regressive. Large numbers of typical enlarged Alzheimer type II cells were observed throughout the region of the substantia nigra, hypothalamus, ventral and lateral thalamic nuclei

and the lenticular and caudate nuclei (figure 7). Large numbers of nuclei were observed having a morphologic resemblance to these Alzheimer cells but intermediate in size between these and the astrocytes. A large number of oligodendroglia was also seen. A few of the typical Alzheimer cells were observed occasionally in the cerebral cortex. When present they were found in the tangential white matter or the deeper layers of the cortex. Despite the glial proliferation there was no evidence of sclerosis nor fiber formation in the Holzer preparations.

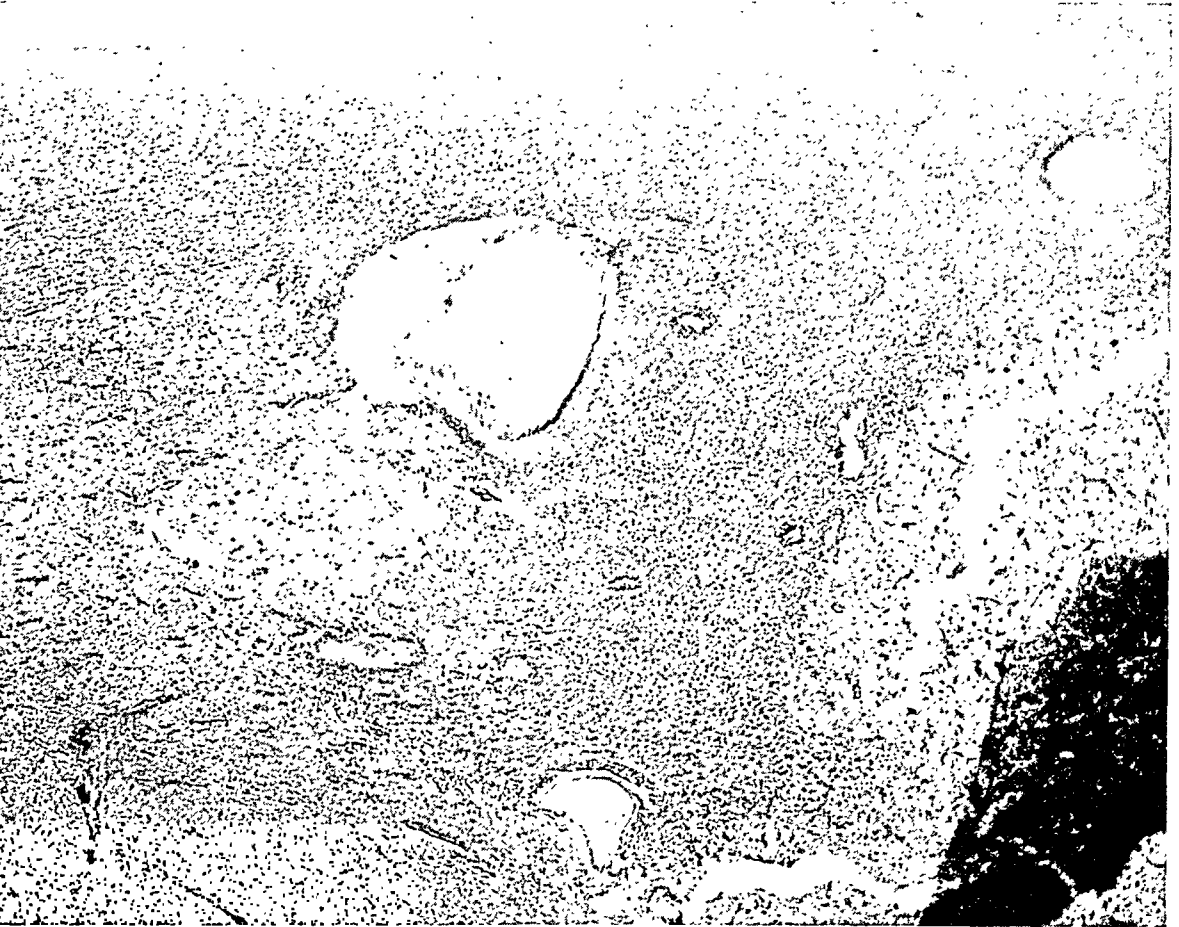


FIG. 6. Necrobiotic segment of caudate seen as darker triangular area with base along ependyma at top and apex extending downward in middle of field. Cajal gold sublimate impregnation. Note relation to large vessels of this region. (Large black area in right lower corner is artefact.) (Low power.)

With the myelin sheath stains one saw frequent, scattered small foci of demyelination throughout the white matter of the cerebral hemispheres and the cerebellum. They bore no evident relation to blood vessels. These foci had fuzzy, irregular borders. There was some early change in the myelin sheaths of the putameno-caudate fibers and a paleness of the fibers in the globus pallidus.

With the Hortega stain, throughout the white matter of the cerebral hemispheres but especially in the tangential regions, regressive changes in the astrocytes were frequently encountered in the form of ameboid glia and, in some cases, a moderate amount of clasmotodendrosis. Occasionally one saw an Alzheimer type II cell

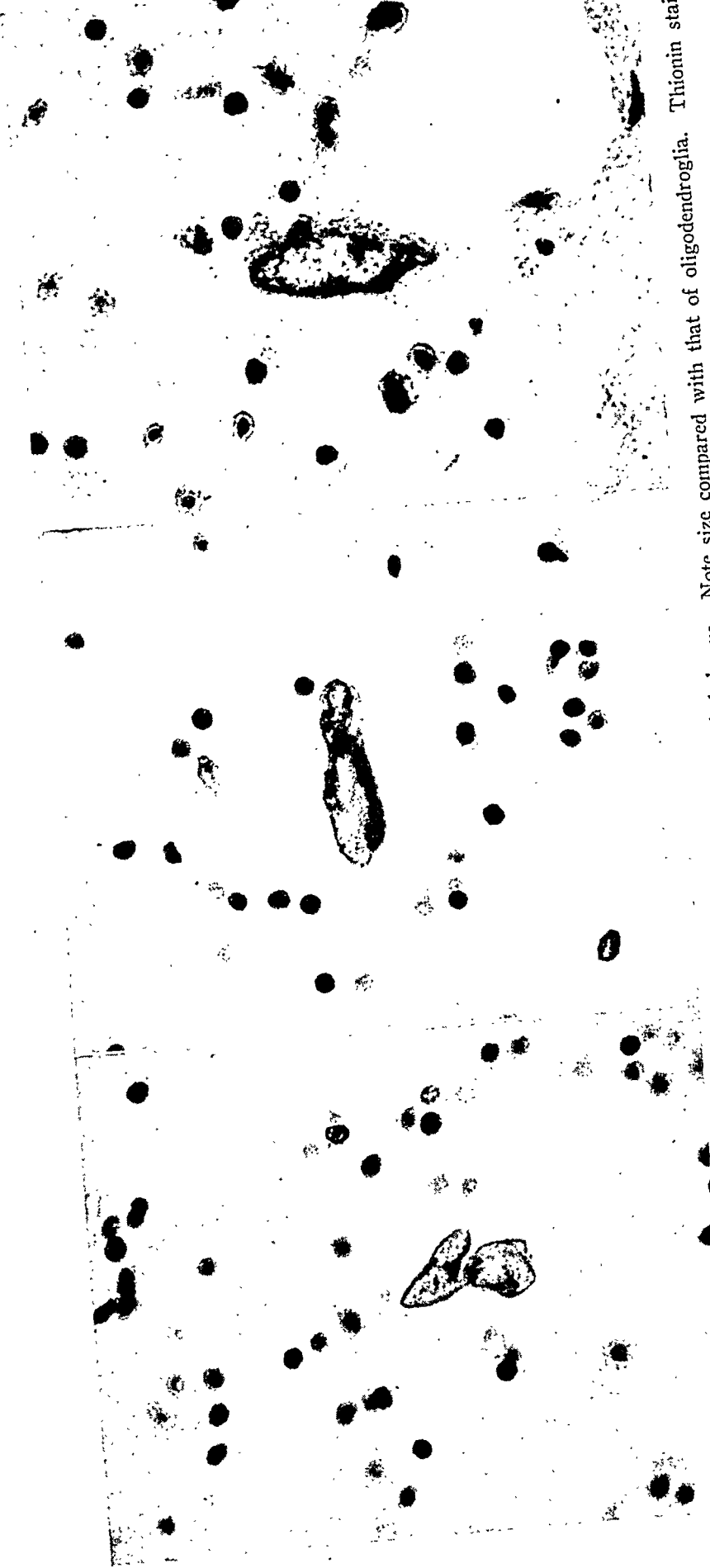


Fig. 7. Alzheimer type II glia cells from various portions of the basal ganglia and thalamus. Note size compared with that of oligodendroglia. Thionin stain. (High power.)

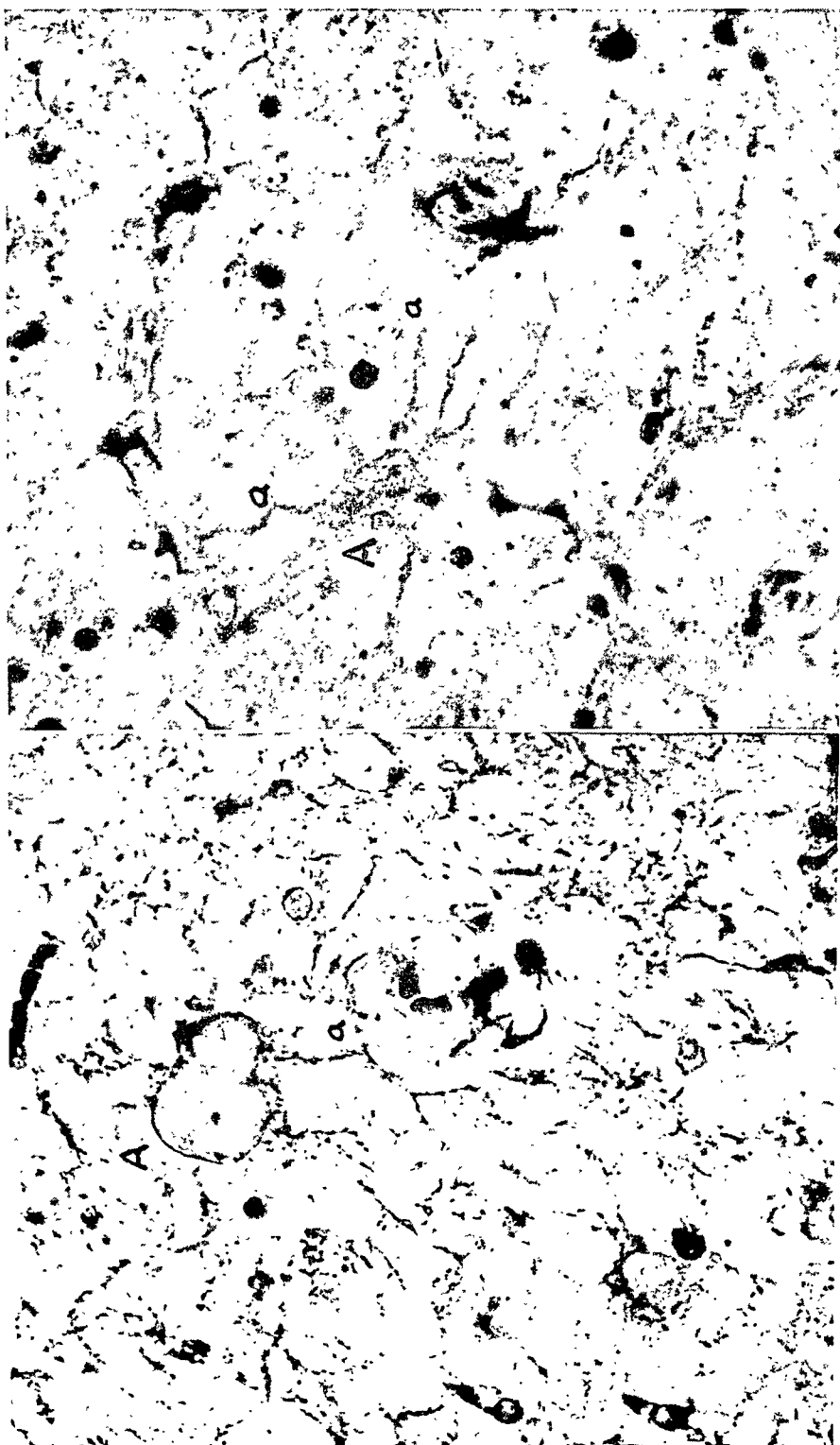


FIG. 8. Alzheimer type II glia from putamen at "A." Hortega silver impregnation. Note clear nucleus with paucity of argentophilic substance. Note vascular extensions in both at "a." (High power.)

among these others. There were also large numbers of oligodendroglia showing acute swelling and a small number of transforming microglia in keeping with the degenerative changes and the number of gitter cells seen. In the basal ganglia there was a similar increase in oligodendroglia undergoing acute swelling, a moderate increase in microglia, some transforming microglia, and a number of hypertrophic oligodendroglia. There was an area of necrobiosis in the caudate nucleus adjacent to the vena terminalis (figure 6), filled with a large number of poorly staining glia cells of the size of astrocytes. The Alzheimer cells were clearly defined in the diencephalon. All of them showed a moderate amount of cytoplasm with numerous processes and in some of them definite sucker feet attachments to the vessels could be discerned (figure 8). In the lenticular nucleus there was a considerable increase in the astrocytes and numerous Alzheimer cells. An apparent increase in capillaries and small vessels could be observed. There was no increase in argentophile reticulum about the vessels.

With the gold sublimate method of Cajal one could see a considerable gliosis in the basal ganglia consisting of astrocytes predominantly of the protoplasmic type. There was moderate clasmotodendrosis and a few monster glia cells were seen. With the Turnbull blue method a few insignificant deposits of iron were observed in the region of the diencephalon and basal ganglia and also some in the choroid plexus. The latter showed frequent areas of vascular hypertrophy in relation to areas of focal fibrosis and scarring.

In summary, apart from the traumatic changes, the disease process was widespread throughout the brain but it was far more severe and advanced in the basal ganglia, the ventral and lateral thalamic nuclei and the hypothalamus. It was characterized by:

1. Primary degeneration of the ganglion cells as indicated by advanced cell changes and earlier relatively slight changes in myelin sheaths and axis cylinders.

2. Considerable glia proliferation, predominantly of the astrocytes, with progressive and regressive changes and with little fiber formation.

3. The transformation of astrocytes into the peculiar large cells of Alzheimer's type II, considered pathognomonic of hepato-lenticular degeneration, which occurred almost exclusively in the basal ganglia and hypothalamus. On the other hand ameiboid glia were numerous in the white matter of the cerebral hemispheres.

4. Reaction of the vascular system in the form of (a) endothelial proliferation of small vessels, most marked in the areas of most advanced cell disease, and (b) scattered small perivascular necroses associated with a spongy state about many of the involved vessels. (Figure 5.)

5. Implication of the ground substance in the disease process as indicated by a spongy state present in the most severely involved regions and resulting in increased friability of the tissue.

6. Lack of any tendency toward repair. Even badly damaged and relatively sessile areas manifested no tissue sclerosis.

DISCUSSION

Clinically the second case manifested the typical features of Wilson's disease. Pathologically, while the changes were diffuse, they were far more marked and advanced in the basal ganglia, thalamus and hypothalamus. In addition, we found in these regions a large number of the type II glial cells of Alzheimer, typical of Wilson's disease and pseudosclerosis. We feel, therefore, that this case must be placed in the category of hepato-lenticular degeneration. While it does not fulfill the original pathologic criteria of

Wilson,¹ namely cystic degeneration of the putamen, nevertheless we do see predominance of degeneration in this region with the formation of a spongy state, and such friability as to lead one to believe that cystic degeneration might ultimately have ensued. At the same time the changes, while diffuse, do not in their pathological characteristics follow the typical descriptions of pseudosclerosis, which include diffuse, widely scattered presence of Alzheimer cells. We may suppose then that we are dealing with a form of hepato-lenticular degeneration intermediate between Wilson's disease and pseudosclerosis.

This case gave us an opportunity to study at some length the staining reactions of the cells of Alzheimer type II. Processes and cytoplasm were observed upon them only infrequently in the Nissl stain, but in the silver and gold preparations these cells had a scanty cytoplasm and definite processes. (Figure 8.) Occasionally sucker feet attachments to vessels could be demonstrated. (Figure 8a.) Furthermore the cells of smaller size but similar appearance seen frequently in the silver and gold preparations closely resembled astrocytes. We feel, therefore, that the origin of these cells is from astrocytes and they represent a progressive change in the latter. In size the nuclei of the typical Alzheimer cells were often two to three times the size of ganglion cell nuclei. In sections from the thalamus, the ganglion cells of this region had undergone a type of degeneration in which there was progressive paling and ultimate disappearance of the cytoplasm but the nucleus remained behind and sometimes appeared to undergo a wrinkling of the nuclear membrane, so that these nuclei at times resembled the small, transitional elements of the Alzheimer type. However, for the reasons given above and from the fact that these cells were frequently found in regions from which the ganglion cells had completely disappeared, it was evident that the Alzheimer cells could not be remnants of ganglion cells. Further, the Alzheimer cell nuclei frequently stained more darkly than the residual ganglion cell nuclei which were pale. Occasionally some of the Alzheimer elements seemed to have a small collection of granular lipoid material within them, suggesting that they may play a small rôle as scavengers.

Of interest is the early spongy state found occasionally in the tangential white matter of the cerebral hemispheres. Barnes and Hurst,² in one of their cases, found extensive cystic degeneration in this region in the frontal lobes. It may be that an early phase of a similar process was developing in our case.

The changes in the cerebral hemispheres were concentrated in the deeper layers of the cortex and the tangential white matter. This destruction appears to bear a relation to the vascular system of the cortex and may support the viewpoint of von Lehoczky³ and others that the pathogenic agent reaches the brain through the circulation.

It is apparent that removal of the spleen was not the primary etiological factor responsible for the onset of hepato-lenticular disease in these cases.

However, there have been other reports of cases in which the syndrome followed splenectomy. Rystedt⁴ reported a case of a girl of 12 years who developed hematemesis, anemia, enlargement of the spleen, and ascites. There were no neurologic symptoms. These symptoms continued and at the age of 15, splenectomy was performed at which time cirrhosis of the liver was noted. At the age of 17 she developed symptoms and signs characteristic of Wilson's disease. Brückner⁵ reported several cases of Wilson's disease of which the first concerned a boy of 16 years who had been ill since the age of nine years with anemia and enlargement of the spleen. This had been progressive and had been diagnosed Banti's disease. In his thirteenth year splenectomy had been performed and at the operation the liver was found to be cirrhotic. Following the operation the first nervous symptoms appeared insidiously in the form of diminished voluntary activity, slowness in movements, stiffness, and heaviness in gait. Two years after the operation he became weak. He was then found to have a constantly smiling facies and to be very restless. Speech was unclear, mouth held open, and there was trouble in swallowing. His course was progressively downhill and he died three months later. Autopsy revealed softening of both lenticular nuclei. Van Bogaert and Willcox⁶ made a study of various types of Wilson's disease. Their first case was that of a boy of 17 years suffering with ascites, upon whom a laparotomy was performed six months later for suspected tuberculous peritonitis. The liver was then found to be very small and hard and nodular, not conforming to any known type of cirrhosis. The spleen was slightly enlarged. He reacted badly to the operation, sank into coma on the third day, and developed rigidity and tremor resembling Parkinsonism. He developed progressive icterus and died on the fifth day. Prior to operation he had had emotional instability, slowness of speech, and trembling during voluntary activity or emotional states. His speech became difficult after the operation and he drooled when he cried. Autopsy revealed symmetrical bilateral degeneration of the caudate nucleus and putamen anteriorly. The operation had aggravated the neurologic and hepatic syndromes in a striking way.

The two patients we present herein developed the complete clinical syndrome of hepato-lenticular disease soon after removal of the spleen. It seems clear that the splenectomy did not initiate the neurological disease. In each case that disease had already existed as shown by: (1) cirrhosis of the liver found at operation, and (2) the existence of minimal neurological symptoms prior to operation, the significance of which had been overlooked. However, the disease was present in a latent or sub-clinical form and the operation seems definitely to have accelerated the process.

The relation of the liver to disease of the brain has been well established. With few exceptions hepato-lenticular disease is associated with hepatic cirrhosis, as first indicated by Wilson¹ and subsequently confirmed by others. Barnes and Hurst,² Greenfield, Poynton, and Walshe,⁷ Van Bogaert and Wilcox,⁶ and others, have shown quite clearly the rôle of liver disease in

this familial disorder. Brouwer⁸ has discussed this problem at some length. Crandall and Weil⁹ have demonstrated degeneration of the basal ganglia in dogs following experimental ligation of the common bile duct. Scherer¹⁰ has shown degenerative changes in the brain, largely involving the glia, in cases of acute yellow atrophy of the liver and in cirrhosis of the liver. Zimmerman and Yannett,¹¹ Fitzgerald, Greenfield and Kounine,¹² and others have shown that following *kernicterus* there may occur well marked degeneration in the brain involving especially the basal ganglia. Brouwer⁸ has emphasized that *kernicterus* is not the result of disease of the liver but is due rather to icterus following severe hemolysis of red blood cells. Nevertheless, it is curious that the pigmentation in the central nervous system involves regions similar to those affected in Wilson's disease. Wilson suggested a possible relationship between preceding *kernicterus* and the disease which now goes properly by his name. It may be that this localization of pigment does impair the resistance of these regions to subsequent noxious agents.

The rôle of the spleen in the pathogenesis of cerebral disease is less clear. In view of the preëxisting disease of the liver in our cases it would seem likely that the spleen played a secondary or precipitating rôle. Somehow the removal of the spleen would appear to have aggravated the latent disease in the liver and thereby to have precipitated the full blown clinical picture. From this point of view we may suppose that an equilibrium had been established between the cirrhosis of the liver and the brain disorder. Minimal subclinical disease existed in the brain in a compensated form. The removal of the spleen served to disrupt this balance with the result that the full blown clinical picture of hepato-lenticular disease developed.

The liver and spleen constitute a major portion of the reticulo-endothelial system of the body economy. It has been suggested by del Rio-Hortega¹³ that the microglia, generally believed to be the mesodermal elements in the brain, may be the reticulo-endothelial elements of the central nervous system. Disease of the liver or removal of the spleen might affect the reticulo-endothelial system as a whole. The microglia should then be involved which would cause the development of disease in the brain. Thus far, however, no one has demonstrated any disease or disturbance of the microglia in hepato-lenticular degeneration and we have found no significant changes in these cells in our case, apart from the rôle which they played in the phagocytosis of products of degeneration. Furthermore, if the microglia played an important part in initiating this disease, one would expect to find diffuse disease of the brain and it would be difficult to explain, on this basis, why the degeneration was confined so strikingly to the basal ganglia.

The pathologic findings in this case, however, indicate that the vascular system was seriously involved in the disease in a widespread fashion but most severely in the basal ganglia. The rôle of the vascular apparatus in cerebral disease is not sufficiently recognized. It seems quite likely that the perivascular histiocytes give rise to the microglia early in embryonic life

(Kershman¹⁴). This is in keeping with the observations of del Rio-Hortega¹³ that the microglia do not appear until the blood vessels in the brain are well formed and that they appear along the paths of the vessels. The sources of the microglia, according to del Rio-Hortega, are mainly the tela choroidea and the pia but also the pial adventitia of the large and medium-sized blood vessels. It seems likely also that the perivascular histiocytes are capable of functioning independently as phagocytes in adult life (Cushing¹⁵).

Very significant, however, is the rôle of the vascular endothelium as the blood-brain barrier (Spatz¹⁶ and others) serving to keep out of the brain particulate matter and perhaps also noxious agents and substances. It is this function which would seem to be most important from the standpoint of protecting the brain from any systemic disease. It may be that the blood-brain barrier is part of the reticulo-endothelial system as a whole and that disease of the liver or spleen could break down this barrier (King¹⁷). *Kernicterus*, already referred to, appears in infants, as King has pointed out, because the blood-brain barrier has not as yet been built up, since in the adult, hemolytic and bile pigments do not enter the parenchyma of the brain. In experimental liver disease the biliary toxins themselves would seem to break down the barrier (Balo and Korpassy,¹⁸ Crandall and Weil⁹). Mahaim¹⁹ studied the changes in the brain following experimental disease of the liver. In two of five dogs he succeeded in establishing chronic changes in the liver. Both animals showed changes in the brain consisting of diffuse ganglion cell disease throughout the brain, but especially striking were vascular changes confined to the striatum. This would support the thesis that the principal effect of liver disease upon the brain may be upon the blood vessels.

In our case the removal of the spleen would seem to be the factor which by disrupting the reticulo-endothelial system led to the breakdown of the blood-brain barrier and the development of lenticular degeneration. The deleterious substances which are immediately responsible for the destruction of brain tissue are not specific but are present in the blood stream as a result of the breakdown of the detoxifying function of the liver. The disturbance in the cerebral vascular system was diffuse throughout the brain but was seen most strikingly in the corpus striatum and especially the neo-striatum. The diffuseness of these changes is in keeping with our thesis. However, why these changes should be so much more severe in and affect to such a greater extent the striatum is still a moot problem.

The question of local vulnerability of the striatum has been discussed by many observers. Kolisko²⁰ attempted to explain the predilection of carbon monoxide poisoning for the striatum by the abnormal character of the circulation to this region. He described the abnormal, backward running course of the branches of the anterior cerebral artery running to this region and he called attention to the fact that the vessels to the lenticular nuclei were end vessels with a rather narrow lumen. Ruge²¹ also emphasized this peculiarity of the circulation to the lenticular nuclei. Spielmeyer²² ex-

pressed similar views. The Vogts²³ have studied this problem in great detail and arrived at their belief in specific pathoclises, suggesting the possibility of chemical or physical peculiarities in the region involved. Spatz¹⁶ emphasized both physical differences depending upon vascular peculiarities and chemical variations.

Brouwer⁸ was forced to the conclusion that, in this disease, there is some congenital weakness or predisposition in this region, indicated by the familial incidence. But the experimental and pathological evidence^{9, 10, 11, 12, 18, 19} would suggest that hereditary factors alone are not the only factors and it may even be that they are not the essential factors. These data would suggest that some local tissue vulnerability, whether physical or chemical, plays an important rôle. That this vulnerability is not a matter of hereditary susceptibility alone is indicated by the findings in *kernicterus* since here, too, there is consistent localization of the staining of brain tissue in the basal ganglia as well as other regions.

It would seem likely that we are dealing with the interrelationship of brain, liver and spleen in an integrated system whose fundamental bond would be the reticulo-endothelial system. The cerebral component of this bond may be the blood-brain barrier. The breakdown of this barrier by disease of the liver or of the spleen or both removes the only protection of the brain against systemic noxious agents and leads to rapid degeneration of the corpus striatum and other regions and results in the development of the clinical picture of hepato-lenticular degeneration.

Both our patients, we feel sure, had previous disease of the basal ganglia. Case 1 had had a Parkinsonian tremor for four years possibly originating in an encephalitis incorrectly diagnosed as typhoid fever. Case 2 had slowed up so much in her work that about a year prior to the operation she had lost her job. In both instances these symptoms attracted little attention and showed no appreciable progression. Following the removal of the spleen, however, in Case 1, the extrapyramidal symptoms increased so rapidly that within two weeks the tremor and rigidity had become intense, and the Kayser-Fleischer ring had developed. In Case 2, increasing striatal symptoms and the Kayser-Fleischer ring were first noticed two months after splenectomy and thereafter the entire clinical syndrome rapidly evolved.

The reticulo-endothelial system, represented by the liver and spleen, was involved in the disorder responsible for the purpura and anemia. At the same time the liver and the striatal system of the brain were implicated in an early, subclinical stage of Wilson's disease since hepatic cirrhosis already existed at the time of the splenectomy. An interrelationship existed between the spleen and liver and between the liver and brain. A delicate balance had been established between these organs. When the spleen was removed this equilibrium collapsed and affected adversely cerebral structures which already had a diminished resistance by virtue of preëxisting disease and a peculiar susceptibility arising from vascular, hereditary, and perhaps chemi-

cal factors. These structures were the corpus striatum especially and to a lesser degree other regions of the brain. The syndrome of hepato-lenticular degeneration then developed.

We recognize that much of our discussion has been speculative. Yet we feel that sufficient data have been presented to warrant our suggestion that removal of the spleen may evoke a quickening of preëxisting latent disease of the brain. One is justified, therefore, in cautioning the surgeon that prior to splenectomy a careful neurological survey should be performed. The possibility that serious disease of the nervous system may follow surgery may be anticipated if such examination reveals evidence of striatal disease.

SUMMARY AND CONCLUSIONS

1. Two cases of hepato-lenticular disease are presented which followed splenectomy performed for symptoms which included purpura and anemia.

2. The pathologic findings are presented and their significance discussed.

3. The relation between the reticulo-endothelial system as represented by the liver and spleen, and structures in the central nervous system is discussed.

4. The histologic findings suggest that Alzheimer type II glia cells arise from astrocytes.

5. A peculiar type of ganglion cell degeneration is noted.

6. Symptoms of disease of the basal ganglia constitute a contra-indication to splenectomy. These structures are a *locus minoris resistentiae* in relation to disease of the reticulo-endothelial system. An operation performed upon the latter may therefore activate disease in the former and lead to hepato-lenticular disease.

BIBLIOGRAPHY

1. WILSON, S. A. K.: Progressive lenticular degeneration, *Brain*, 1912, xxxiv, 295.
2. BARNES, S., and HURST, E. W.: Hepato-lenticular degeneration, *Brain*, 1925, xlviii, 279.
3. VON LEHOCZKY, T.: Zur klinischen und anatomischen Diagnose der Wilson-pseudo-sklerose Krankheit, *Deutsch. Ztschr. f. Nervenhe.*, 1936, cxli, 28.
4. RYSTEDT, G.: Case of Wilson's disease, *Acta med. Scand.*, 1923, lix, 377.
5. BRÜCKNER, J. M.: Bilateral progressive degeneration of lenticular nuclei, *Jahrb. f. Kinderh.*, 1925, cx, 284.
6. VAN BOGAERT, L., and WILLOX, E.: Dégénérescence hepato-lenticulaire, *Rev. Neurol.*, 1936, lxvi, 461.
7. GREENFIELD, J. G., POYNTON, F. J., and WALSHE, F. M. R.: On progressive lenticular degeneration, *Quart. Jr. Med.*, 1923-4, xvii, 385.
8. BROUWER, B.: Spleen, liver, and brain, *Proc. Roy. Soc. Med.*, 1936, xxix, 579.
9. CRANDALL, L., and WEIL, A.: Pathology of the central nervous system in disease of the liver, *Arch. Neurol. and Psychiat.*, 1933, xxix, 1066.
10. SCHERER, H. J.: Relation between liver and brain changes, *Virchow's Arch. f. path. Anat.*, 1933, cclxxxviii, 333.
11. ZIMMERMAN, H. M., and YANNETT, H.: Kernicterus, *Am. Jr. Dis. Child.*, 1933, xlv, 740.
also: Cerebral sequelae of icterus gravis neonatorum, *ibid.*, 1935, xlix, 418.
12. FITZGERALD, G. M., GREENFIELD, J. G., and KOUNINE, B.: Neurological sequelae of kernicterus, *Brain*, 1939, lxii, 292.

13. DEL RIO-HORTEGA, P.: Microglia, *in* PENFIELD, W.: Cytology and cellular pathology of the nervous system, 1932, Paul B. Hoeber, Inc., New York, ii, 483, 487.
14. KERSHMAN, J.: Genesis of microglia in the human brain, Arch. Neurol. and Psychiat., 1939, xli, 24.
15. CUSHING, H.: The third circulation, Cameron Lectures, 1925, Edinburgh.
16. SPATZ, H.: Über Stoffwechseleigentümlichkeiten in den Stammganglien, Ztschr. f. d. ges. Neurol. u. Psychiat., 1922, lxxviii, 641.
17. KING, L. S.: Hematoencephalic barrier, Arch. Neurol. and Psychiat., 1939, xli, 51.
18. BALO, J., and KÖRPASSY, B.: Encephalitis of dogs with Eck fistula fed on meat, Arch. Path., 1932, xiii, 80.
19. MAHAJIM, I.: Hepato-lenticular degeneration, Schweiz. Arch. Neurol. u. Psychiat., 1925, xvi, 252, and xvii, 43, and 283.
20. KOLISKO, A.: Beiträge zur Kenntnis der Blutversorgung d. Grosshirnganglien, Wien. klin. Wchnschr., 1893, vi, 191.
21. RUGE: Quoted by Brückner.
22. SPIELMEYER, W.: Anatomic substratum of the convulsive state, Arch. Neurol. and Psychiat., 1930, xxiii, 869.
23. VOGT, C., and O.: Erkrankungen der Grosshirnrinde im Lichte der Topistik, Pathoklise, und Pathoarchitektonik, 1922, J. A. Barth, Leipzig.

THE QUANTITATIVE SEROLOGIC TEST FOR SYPHILIS; ITS VARIABILITY, USEFUL- NESS IN ROUTINE DIAGNOSIS, AND POSSIBLE SIGNIFI- CANCE; A STUDY OF 1665 CASES *

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THE complement fixation reaction for the diagnosis of syphilis was introduced by Wassermann, Neisser, and Bruck in 1906; and the foundation of modern flocculation technics was laid by Michaelis in 1907. These originators used a fixed amount of patient's serum, a qualitative procedure still used in most serodiagnostic laboratories. The amounts of patient's serum used in the standard qualitative diagnostic tests commonly employed in the United States are shown in table 1. Because of the widely different types

TABLE I

The Amounts of Patient's Serum Used in the Standard Qualitative Diagnostic Tests Used in the United States for the Serodiagnosis of Syphilis *

Test	Amount of Patient's Serum Employed †
Eagle flocculation	0.2-0.1 c.c.
Eagle complement fixation	0.2-0.1 c.c.
Hinton flocculation	0.5 c.c.
Kahn standard and presumptive flocculation	0.15 c.c.
Kline diagnostic and exclusion flocculation	0.05 c.c.
Kolmer complement fixation	0.2-0.1 c.c.

* Revised technics of the Eagle, Hinton, Kahn, Kline, and Kolmer tests; from "The Serodiagnosis of Syphilis," Ven. Dis. Inform., Supp. No. 9, pp. 155-224.

† In all these technics, the critical factor is the serum: antigen ratio, rather than the absolute amounts of either. The amounts of serum indicated in the table are those used with a fixed amount of antigen, the type and volume of antigen suspension used differing in the individual technics. A rough quantitation may be introduced into any of these tests by the use of decreasing amounts of serum in the same total volume (i.e., increasing serum dilutions), with a fixed amount of antigen (cf. quantitative Eagle, Kahn and Kolmer technics).

of "antigen" suspension used in these tests, and because the serum: antigen ratio rather than the absolute amount of serum is the critical factor, the figures indicated in table 1 are in no sense a measure of the relative sensitivity of the several technics. The results of the test, referred to these fixed amounts of serum, are commonly reported as "positive," "doubtful" and

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"negative," or alternatively, in terms of plus marks or figures, "++++" ("4") or "+++" ("3") usually taken to mean "positive," "++," "+," or " \pm " ("2" or "1") usually taken to mean "doubtful," and "0" meaning "negative." These are standard "qualitative" serodiagnostic tests.

However, as was first shown by Boas² in 1909, "the positivity of syphilitic sera varies between extraordinarily wide limits: some sera contain barely enough reagin to give a positive or doubtful reaction when 0.2 c.c. of whole serum is used in the test, while others contain 100, 200, or even 400 times this minimal 'fixing' quantity" (Eagle³). The reagin titer may be determined, as may the serum agglutinin titer against bacteria, by using graded quantities of serum in a series of tubes (Boas² 1909, Noguchi⁴ 1911) expressing the result as the highest dilution of serum which gives a positive result, or alternatively by the indirect method of adding increasing amounts of complement to a constant quantity of serum and antigen (Gehrmann, Wesener, and Roman⁵; Browning and McKenzie⁶; Swan⁷; Wadsworth, Maltaner, and Maltaner⁸). These are "quantitative" serodiagnostic tests for syphilis.*

Most workers have approached this question from the purely serologic point of view, and have described one or another technic of quantitation. Such papers do not here concern us, except in so far as it is necessary to emphasize, as Duke⁹ pointed out in 1922, that the reagin "titer" obtained in any given serum varies with the technic, e.g., a serum which contains 400 units of reagin by one procedure might show only 40 units with a less sensitive technic, or 1600 units by a more sensitive technic. Quantitative tests on a given serum are therefore comparable only when carried out by the same technic in the same laboratory, and even then are only roughly comparable, due to unavoidable day-to-day variations in sensitivity (Mohr and Smith¹⁰).

Sporadic and for the most part small scale studies of the clinical applicability of quantitative serodiagnostic tests have been made by various observers since 1909 (e.g. Duke,⁹ Osmond,¹¹ Phillips and Litterer,¹² Lorenz,¹³ Simpson,¹⁴) without, however, presenting data which justified their routine application in the diagnosis or treatment of syphilis, or their routine adoption by serodiagnostic laboratories. Apparently only two investigators have studied any considerable series of patients with quantitative serologic tests (Vedder¹⁵ 281 cases, Schwartz¹⁶ 142 cases). Both Vedder and Schwartz agree that "although certain clinical conditions are *generally* associated with a high titer and others with a *generally* low titer, the individual variations are so pronounced as to make the actual titer of no diagnostic significance in the particular case."³ However, it has been suggested (Vedder,¹⁵ Moore¹⁷) that the character and extent of the quantitative serologic response to treatment may ultimately prove to be of prognostic, if not of diagnostic, importance.

* The present paper is a discussion of quantitative serologic testing as applied to blood serum only, and does not apply to quantitative tests on cerebrospinal fluid.

In spite of the work of Vedder and Schwartz, attention has been recently sharply focused on quantitative serologic testing as an aid in the diagnosis of syphilis by the several papers of Wadsworth and his associates,⁸ by the recent adoption of a quantitative technic as a routine procedure in the New York State Department of Health Laboratories, and by a still more recent communication from Kahn.¹⁸

Both Wadsworth and his associates and Kahn assume as definitely proved, though neither documents the assumption, that the more strongly positive the quantitative test, the more "active" and presumably the graver is the patient's syphilitic infection, and thus, the greater the diagnostic significance of the positive result. Thus Wadsworth says, "As a rule the higher the titer, the greater its significance in diagnosis," and also, "These quantitative procedures yield numerical values indicating the extent of the specific activity of the serum which the clinician uses simply as an aid to diagnosis in the true sense." Similarly, Kahn says: "The concentration of antibodies . . . is believed to depend on the degree of syphilitic activity in the patient, on his capacity to produce antibodies, and upon other factors. . . . All indications are that low, moderate, and high titers correspond, in most instances, to low, moderate, and marked syphilitic activity."*

It is possible, however, that the reagin content of the blood of an individual patient or of groups of patients with various clinical conditions due to syphilis may be dependent on a variety of factors. On a purely speculative basis, some of these may be enumerated as follows:

- (1) Possible variations in the strain of the infecting organism.
- (2) The number of organisms present in the tissues of the host, and thus, the amount of antigenic material available as a stimulus for antibody production.
- (3) The duration of infection.
- (4) The particular tissue or tissues predominantly involved, the approximate extent of their involvement, and the intensity of the inflammatory reaction.
- (5) The capacity of the host to develop an immune response.
- (6) Antisyphilitic treatment.

* Kahn suggests further that the quantitative serologic test should be of value in the following circumstances:

- (1) In the diagnosis of questionable cases lacking history or physical evidence of syphilis. Here high titers should be of greater diagnostic value than low titers.
- (2) In the study of positive serologic reactions produced by diseases other than syphilis.
- (3) In following the effects of antisyphilitic treatment.
- (4) In predicting impending clinical relapse in patients under treatment.
- (5) In seroresistant cases.
- (6) In the interpretation of therapeutic tests.

These and other circumstances in which quantitation seems valuable under conditions of present knowledge will be discussed in a later paper.

(7) Various extraneous factors such as race, age, sex, pregnancy, the season of the year, and perhaps many others.

PURPOSE OF THIS STUDY

The growing use of quantitative procedures in serodiagnostic laboratories, and the apparent complexity of their interpretation, seemed to warrant a restudy of the serum reagin titer in various stages of syphilis on a larger scale than was attempted by Schwartz¹⁶ and by Vedder.¹⁵ In particular, it seemed important to ascertain whether there was any demonstrable correlation between the serum reagin content and the degree of syphilitic activity, as stated by Kahn¹⁸ and implied by Wadsworth and his associates.⁸

Quantitative serologic testing by the Eagle complement fixation technic has been under investigation in the Syphilis Division of the Johns Hopkins Hospital since 1928. The quantitative test has been used both in diagnosis and treatment. A body of experience has thus been accumulated which permits the examination of some of the factors which may conceivably influence the reagin content of the blood. Certain of these will be discussed in this and subsequent papers, together with our opinion of the value of routine quantitative tests in diagnosis and treatment.

METHODS AND MATERIALS

The serologic technic employed was that described by Eagle,³ in which the reagin titer is arbitrarily expressed as the highest dilution of serum which gives a positive result: e.g., if the test is positive with serum diluted 1-2, but negative in 1-4 and higher dilutions, there are said to be 2 units of reagin. Arbitrary interpolation is permissible, e.g., if a serum is positive in 1-64, doubtful in 1-128, and negative in 1-256 dilutions, the titer is said to be 96 units. Actual interpolation of dilutions was often carried out when exact titration was desired.

Two laboratories, each using the same technic, were utilized in this study, one the serologic laboratory of the Johns Hopkins Hospital, the other a private laboratory. Each is under the joint personal supervision of both authors.

As has been pointed out from this clinic by Mohr and Smith,¹⁰ the daily variations frequently observed in the serum reagin titer of individual patients usually depend, not on actual variations in the reagin content of the serum, but on daily fluctuations in the sensitivity of the technic employed. These daily technical variations may be obviated by freezing samples of serum as obtained from a given patient on different days, keeping the specimens in the frozen state (-25° C.) until the termination of the experiment, and testing all the specimens on the same day with the same reagents (a procedure not followed in the material presented in these studies). Further, such daily variations may be minimized by the use of a quantitative flocculation instead

of a complement fixation technic. Even with a quantitative complement fixation technic, which we have now abandoned in favor of a quantitative flocculation technic, daily variations have been less a problem in the private laboratory used in this study than in the hospital laboratory, for various technical reasons. With due technical care, remarkably constant quantitative results may be obtained in a given patient over a period of years.

The Eagle complement fixation test as used in both laboratories of this study is perhaps 10 per cent less sensitive in an overall syphilitic population, treated and untreated, than the Eagle or Kline diagnostic flocculation tests which are run in parallel with it, and is in our hands of the same order of sensitivity as the Kahn standard flocculation test. It follows that a number of patients, serologically recognizable as syphilitic by virtue of positive flocculation tests, nevertheless have simultaneously negative complement fixation tests and therefore a titer of 0 as defined in the present study. This fact is apparent in the following tables.

CLINICAL MATERIAL

All new patients admitted to the Syphilis Clinic of the Johns Hopkins Hospital or seen in private practice by one of us over the 12 years covered by this study have been routinely tested with the quantitative complement fixation procedure. The technic has been further used throughout the course of treatment in patients with early syphilis, both clinic and private, and in unselected cases of late syphilis, the latter only in private practice.

EXPERIMENTAL RESULTS

The Quantitative Reagin Titer in Previously Untreated Early Syphilis: There were available for study 508 cases of previously untreated early syphilis (106 primary, of which 33 were seronegative and 73 seropositive, and 402 secondary). The distribution of these according to initial reagin titer is given in table 2. There was a rough relationship of titer to duration of infection, in that the mean and median titers in primary syphilis were lower than in secondary syphilis (primary syphilis mean 104.3 ± 13.74 units, median 43.2 ± 17.22 units; secondary syphilis, mean 179.6 ± 7.54 units, median 142.3 ± 9.45 units). As will be shown in a subsequent paper of this series (Crosby and Campbell¹⁹), however, the influence of the duration of infection on the reagin titer, even in primary syphilis, is a highly irregular one, and in secondary syphilis there is no constant relation.

Even in secondary syphilis, where reagin titer is presumably at its maximum, there were wide variations in titer in individual cases. The majority (65 per cent) were strongly positive (101 units or more), but in an appreciable number very low titers were obtained. Obviously, therefore, the titer of the serum is not a useful guide in diagnosis, which is as certain as in a case with only 2 units as in one with 1600 units (the highest titer observed).

In a following paper of this series, by Crosby and Campbell,¹⁹ will be considered the relationship of the serum reagin titer in early syphilis to such factors as race, sex, age, pregnancy, severity of lesions, response to early treatment, and similar considerations which are beyond the scope of this paper.

The Quantitative Reagin Titer in Previously Untreated Late Syphilis: Although the quantitative test has been applied on admission to about 3,000 patients with late syphilis, only 1157 patients, selected at random from the total, and including various types of late syphilis as hereafter described, form the basis of this study. The difficulty of determining the value of quantita-

TABLE II

The Quantitative Titer of Reagin in 508 Patients with Previously Untreated Early Syphilis

Units of Reagin	Primary Syphilis		Secondary Syphilis	
	Cases	Per cent	Cases	Per cent
0	33	29.8	4	0.9
0.5-4	10	9.6	5	1.2
5-12	1	0.9	8	1.9
13-18	1	0.9	11	2.7
19-25	4	3.8	13	3.2
26-37	2	1.9	14	3.4
38-50	5	4.8	18	4.4
51-75	3	2.8	23	5.7
76-100	7	6.7	43	10.7
101-150	12	11.5	75	18.6
151-200	10	9.6	76	18.9
201-400	14	13.4	82	20.3
400+	4	3.8	30	7.2
Total	106	99.5	402	99.3
Mean titer (grouped) \pm standard error	104.33 \pm 13.74		179.63 \pm 7.54	
Median titer (grouped) \pm standard error	43.20 \pm 17.22		142.33 \pm 9.45	

tive serologic tests in late as contrasted with early syphilis (all of whom had received no treatment before admission) lay in assembling a sufficiently large group of patients with late syphilis not previously treated. Only 445 patients in this group of 1157 had received no previous treatment; the remaining 712 had had varying amounts of treatment before admission, ranging from a single injection of an arsphenamine 20 years previously to several years of thoroughly adequate treatment just preceding admission. No attempt was made in the latter group to study the effect of the time and duration of preceding treatment on the reagin titer, though obviously treatment as a whole is a factor which must be taken into account.

To consider first the previously untreated patients, the 196 diagnosed as latent syphilis had no clinical evidence of syphilis detectable on complete and careful physical examination. Almost without exception, their spinal fluids were examined and were found to be normal. Excluding neurosyphilis, there were 69 patients with previously untreated late syphilis presenting a wide variety of lesions, e.g., cutaneous, osseous, visceral, cardiovascular. The number of patients is clearly too small to warrant any subdivision on the basis of the tissue structures involved. For valid conclusions as to the reagin titer in the various forms of late syphilis, e.g., osseous as opposed to cardiovascular, many more cases should be studied, in whom the factor of previous treatment can be eliminated. Finally, there were 180 cases of previously untreated neurosyphilis, subdivided into cases with diffuse meningovascular involvement (59), tabes (77), and paresis (44).

The results in these 445 cases of late untreated syphilis are summarized in table 3. It is obvious at a glance that within each group there were wide variations in reagin titer, the actual values ranging between 0 and 400 units.

TABLE III

The Quantitative Titer of Reagin in 445 Patients with Previously Untreated Latent, Late, and Neurosyphilis

Units of Reagin	Latent Syphilis (no clinical evidence of disease, C. S. F. negative)		Late Syphilis (all forms except neurosyphilis; mostly benign late and cardiovascular)		Neurosyphilis					
					Diffuse Meningovascular		General Paresis (including taboparesis)		Tabes Dorsalis	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
0	25	12.3	13	18.8	6	10.1	5	11.3	14	18.1
0.5-2	11	5.6	3	4.3	1	1.6	3	6.8	8	10.4
3-5	26	13.3	2	2.8	3	5.0	3	6.8	10	13.0
6-10	40	20.5	10	14.5	16	27.1	4	9.0	16	20.7
11-20	23	11.7	8	11.5	16	27.1	7	15.8	5	6.5
21-40	28	14.6	15	21.7	4	6.7	11	25.0	11	14.2
41-60	21	10.7	4	5.8	2	3.4	5	11.3	1	1.3
61-80	8	4.1	3	4.3	3	5.0	1	2.2	11	14.2
81-100	6	3.0	3	4.3	1	1.6	3	6.8	—	—
101-150	8	4.1	1	1.4	3	5.0	2	4.5	1	1.3
151-200	—	—	6	8.6	4	6.7	—	—	—	—
201-400	—	—	1	1.4	—	—	—	—	—	—
400+	—	—	—	—	—	—	—	—	—	—
Total	196	99.9	69	99.4	59	99.3	44	99.5	77	99.7
Mean titer (ungrouped) ± standard error	26.5 ± 2.5		44.1 ± 7.9		37.2 ± 7.2		33.14 ± 5.57		21.2 ± 3.3	
Median titer (ungrouped) ± standard error	11.5 ± 3.1		19.5 ± 9.8		13.75 ± 9.0		25.0 ± 7.0		10.64 ± 4.15	

It is further obvious, and confirmed by the statistical analysis, that there was no correlation whatever between the type or gravity of the syphilitic infection and the serologic titer.

Comparing the five groups of previously untreated patients here considered (latent, benign and cardiovascular, diffuse meningovascular neurosyphilis, tabes and paresis), the latent syphilitics and tabetics form one group, with mean titers of 26.5 and 21.2 respectively, and the other three categories form a second group with mean titers of 44 for benign late and cardiovascular syphilis, 37.5 for meningovascular neurosyphilis, and 33 for paresis. The differences between the two broad groups are approximately twice the standard error of the difference, and therefore, on the borderline of statistical significance. Similarly, the medians of these groups (11.5 ± 3.1 and 10.64 ± 4.15 for latent syphilis and tabes respectively, and 19.5 ± 9.8 , 13.75 ± 9.0 and 25.0 ± 7.0 for benign late and cardiovascular, meningovascular neurosyphilis and paresis) do not differ significantly, this despite the wide differences in the degree of pathologic involvement, clinical incapacitation, and ultimate prognosis represented by these five diagnostic categories.

The Effect of Previous Treatment on Quantitative Titer: The effect of previous treatment on titer in late syphilis is shown in table 4, where are com-

TABLE IV

The Mean and Median Serologic Titer in Late Syphilis as Affected by Treatment Received Prior to Admission

Diagnosis	No Previous Treatment			Previous Treatment		
	Cases	Titer		Cases	Titer	
		Mean	Median		Mean	Median
Latent	196	26.5	11.5	228	7.0	0.0
Late (benign late and cardiovascular)	69	44.1	19.5	110	23.5	4.6
Meningovascular neurosyphilis (including asymptomatic)	59	37.5	13.8	140	16.5	3.8
General paresis	44	33.1	25.3	97	27.5	9.7
Tabes dorsalis	77	21.2	10.6	137	11.7	1.6

pared the mean and median titers in 712 patients with various types of late syphilis who had been treated at some time and in some amount before the quantitative test was performed, as compared with the 445 patients with similar clinical diagnoses who had received no previous treatment. For the most part (except in the patients diagnosed as latent syphilis) this previous treatment had been ineffectual in controlling symptoms or preventing progression or relapse; and the patients with benign late, cardiovascular, or central nervous system syphilis of various types, who had been previously treated, were as ill on admission as those patients who had received no treat-

ment. Nevertheless, the previous treatment had resulted in halving the mean serologic titer and in reducing to an even greater extent the median titer of all forms of late syphilis except general paresis. This reduction in titer, therefore, was not paralleled by clinical improvement and apparently did not represent a lessened severity or gravity of the syphilitic process.

DISCUSSION

The Value of Quantitative Serologic Testing in Routine Diagnosis: The data presented permit certain broad generalizations. The reagin content of the blood is much higher in early than in late syphilis. In the early weeks of infection there is, as might be expected, a progressive increase in titer until the secondary outbreak appears. Thereafter, as will be subsequently shown in more detail by Crosby and Campbell,¹⁰ the median titer remains approximately unchanged during the secondary stage. As years, rather than months, go by and even though no treatment is given, the titer falls gradually or abruptly, and in all the types of late syphilis is on the whole only from 1/5 to 1/10 as great as in the early months.

These are, however, generalizations based on average titers. In all stages of syphilis, even during the secondary outbreak, there are wide individual variations in reagin content. Thus, a median titer of 19.5 and a mean titer of 44, such as were observed in 69 untreated cases of late syphilis, have little absolute significance when the individual titers varied from 0 to 400, and the standard error of the median and mean amounted to 9.8 and 7.8, respectively. Moreover, previous treatment, in any amount or at any time relative to serologic testing, may markedly reduce the serum reagin content, even though clinical improvement does not occur.

These facts indicate clearly that quantitative serologic testing is of little or no value in the routine serologic diagnosis of syphilis. The reagin titer usually furnishes no important additional information. The particular circumstances in which quantitative serologic tests are of clinical significance will be discussed in a separate paper.

THE POSSIBLE CAUSES OF VARIATION IN REAGIN TITER

There is no real evidence of serologically different strains of *T. pallidum*, and it is accordingly idle to speculate whether the reagin titer may vary according to the strain of the infecting organism. It is generally supposed, on what seems to be good evidence, that the generally higher reagin titers observed in early syphilis are due to the fact that the tissues of the host contain enormous numbers of treponemes, the majority of which are thought to be destroyed by the body's own defenses concomitant with the spontaneous healing of the early lesions. Thus, in untreated syphilis in the rabbit, the serum reagin content rises as the initial testicular syphiloma develops, and falls coincident with or shortly after its spontaneous resolution. If the

syphiloma is excised before the tissue reaction has reached its height, the reagin content of the blood also falls, only to show a secondary rise as organisms multiply elsewhere in the body (Kemp, Chesney, and Poole²⁰). In human early syphilis also, it is apparently true that the reagin titer generally increases as the numbers of organisms increase, reaching a maximum at the time of the secondary outbreak. What happens to the reagin titer in human beings coincident with the spontaneous healing of secondary syphilis is of course unknown.

These relationships of reagin content to the number of organisms and the duration of infection are, however, applicable only to the early months of the disease. In late syphilis of more than 2 to 4 years' duration no such relationship is apparent. The reagin content is as high, on the average, in those who have had syphilis for 20 years as in those infected for only 5 to 10 years. No conjectures are permissible, moreover, as to the relative number of organisms present in the tissues in various forms of late syphilis, with the possible exceptions of *tabes dorsalis* where they are usually few (at least in the nervous system) and in general paresis where they are usually many (in the brain). Perhaps the somewhat lower average reagin titer in *tabes dorsalis* and in latent syphilis as compared with other late complications, is mildly confirmatory of the hypothesis that even in late syphilis, the reagin titer may be influenced by the number of organisms in the tissues.

The data of this paper do not permit any statements regarding the possible relationship of reagin titer to the involvement of particular tissues or to the extent of that involvement. Our own material, and that of all previously reported series, is far too small for this purpose; while the complicating factor introduced by the variable number of organisms present in the tissues would render the analysis of dubious significance.

Neither in the individual patient nor in groups of cases of various types of syphilis is there any indication that reagin titer before treatment is an expression of resistance to infection. A single titered test, whether the reagin content is high or low, has therefore no prognostic value. True, Moore and Kemp²¹ have shown that in patients with early secondary syphilis whose serologic tests before treatment were incompletely positive, or who became seronegative with unusual rapidity after treatment,* clinical relapse was 4 to 5 times more frequent than in the entire group of patients with early syphilis. It is nevertheless clear that the reagin titer as such, considered as an isolated finding, is not a direct expression of the degree of immunity or of resistance to infection. If it were, one might expect the titer to be at its highest in patients with long standing latent syphilis, in whom no lesions have developed in spite of the passage of many years. This is not the case. The titer is far less in late latent syphilis than it is in early syphilis, and is comparable with that found in various forms of late syphilis with clinical mani-

* Though a quantitative technic was not then used, such patients probably had low reagin titers.

festations. It may be that the behavior of reagin titer during and after treatment, and both in early and late syphilis, may offer an expression of the patient's immunity and may prove to be of prognostic importance. However, to determine this fact will require years of observation of many patients.

The influence of antisyphilitic treatment on reagin titer has been discussed for early syphilis by Moore and his associates²² and by others. It is further demonstrated in this paper that in late syphilis, also, previous treatment in varying amounts and at various times significantly reduces the reagin content of the blood, even in the absence of concomitant clinical improvement.

Various extraneous factors which may influence reagin titer such as race, sex, pregnancy, and others will be discussed, so far as early syphilis is concerned, in the next paper of this series.

SUMMARY

1. The serum of syphilitic patients contains varying quantities of reagin. Quantitative serologic tests to determine this reagin "titer" are comparable only when carried out in the same laboratory by the same technic; and even then, the results may be modified by day-to-day variations in the sensitivity of the test.

2. The quantitative reagin titer of the blood in 508 patients with early syphilis, determined by a complement fixation technic, varied from 0 to 1600 units of reagin. In primary syphilis, the mean titer was 104.3 ± 13.74 units, the median 43.2 ± 17.22 units; in secondary syphilis the mean was 179.6 ± 7.54 and the median $142.3 \pm (9.45)$ units.

3. In 445 patients with various forms of untreated late syphilis, the quantitative titer ranged from 0 to 1600 units. These patients were separated into 5 groups: (a) latent syphilis, (b) various forms of late syphilis (excluding neurosyphilis), (c) diffuse meningovascular neurosyphilis, (d) general paresis, (e) tabes dorsalis. In these groups, the mean titers ranged from 21.5 to 44.1 units, the medians from 10.7 to 25 units, i.e., significantly lower than in early syphilis. It is suggested by these data, though not yet definitely proved, that patients with late latent syphilis and tabes dorsalis may have significantly lower serologic titers than patients with other types of late syphilis.

4. In late syphilis, previous treatment in any amount and at any time before quantitative testing significantly reduced the mean and median titers in the 712 such patients tested. This reduction was not necessarily associated with clinical improvement.

5. Quantitative serologic testing is of little value as a routine diagnostic procedure.

6. The reagin titer of the blood is not an expression of the severity or gravity of syphilitic infection in the individual patient. Enormous variations in titer are observed in all types of clinical involvement (0-1600), in-

cluding both early and latent syphilis; and the reduction in titer effected by treatment is not necessarily associated with clinical improvement.

7. The reagin titer appears definitely to be related to the numbers of organisms present in the tissues of the host, since titers were higher in early than in late syphilis. As between various types of late syphilis, however, no such conclusion is permissible. There is no evidence available as to the possible relationship of reagin titer to the involvement of particular body tissues.

8. The effect of prolonged treatment on the rate of fall of reagin titer may conceivably be an expression of the immunity or resistance of the host; but even if this were true, a single quantitative test before treatment would be of no diagnostic or prognostic importance. Further studies of the behavior of reagin titer under prolonged treatment are essential to settle the possible prognostic value of such serial quantitative tests.

9. Subsequent papers will consider (a) certain extraneous factors which may influence reagin titer, (b) the circumstances in which quantitative serologic testing is known to be useful in diagnosis and treatment.

BIBLIOGRAPHY

1. See first footnote, table 1.
2. BOAS, H.: Die Wassermannsche Reaktion bei aktiven und inaktiven Sera, Berl. klin. Wchnschr., 1909, xlv, 400.
3. EAGLE, H.: Laboratory diagnosis of syphilis, 1937, C. V. Mosby Co., St. Louis, Mo., p. 86.
4. NOGUCHI, H.: Die quantitative Seite der Serodiagnostik der Syphilis, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1911, ix, 6.
5. GEHRMANN, A., WESENER, J. A., and ROMAN, M.: The prognostic and diagnostic value and interpretation of the quantitative Wassermann reaction, Ill. Med. Jr., 1921, xxxix, 212.
6. BROWNING, C. H., and MCKENZIE, I.: Recent methods in the diagnosis and treatment of syphilis, 1924, Constable & Co., London.
7. SWAN, M. H.: Three phases of the Wassermann technic, Jr. Lab. and Clin. Med., 1926, xii, 865.
8. (a) WADSWORTH, A., MALTANER, F., and MALTANER, E.: Quantitative studies of the complement-fixation reaction with syphilitic serum and tissue extract, Jr. Immunol., 1938, xxxv, 105.
(b) *Ibid.*: Technic of the practical quantitative test, Jr. Immunol., 1938, xxxv, 217.
(c) MALTANER, E.: Serologic tests in the diagnosis of syphilis, Am. Jr. Pub. Health, 1939, xxix, 104.
9. DUKE, W. W.: Interpretation of the Wassermann reaction, Arch. Int. Med., 1922, xxx, 531. The quantitative Wassermann in relation to the diagnosis and treatment of syphilis, Ann. Clin. Med., 1923, ii, 137.
10. MOHR, C. F., and SMITH, C. A.: On the supposed daily variation of the reagin content of syphilitic serum, Am. Jr. Syph., Gonor. and Ven. Dis., 1940, xxiv, 322.
11. OSMOND, T. E.: Quantitative serum tests in syphilis, Brit. Jr. Ven. Dis., 1935, xviii, 248.
12. PHILLIPS, K., and LITTERER, A. B.: The clinical value of quantitative blood studies in the management of syphilis, including fever therapy, Urol. and Cutan. Rev., 1939, xliii, 58.
13. LORENZ, W. F.: Clinical use of quantitative blood tests (adaptation of Eagle's micro-flocculation test), Wis. Med. Jr., 1938, xxxvii, 281.

14. SIMPSON, W. M.: Artificial fever therapy of syphilis, *Jr. Am. Med. Assoc.*, 1935, cv, 2132.
15. VEDDER, E. B.: The intensity of the positive Wassermann reaction as a guide to treatment, *Mil. Surg.*, 1929, lxxv, 195.
16. SCHWARTZ, S. C.: Reagin content of serum in various manifestations of syphilis, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1931, xv, 387.
17. MOORE, J. E.: The modern treatment of syphilis, 1933, Charles C. Thomas, Springfield, Ill.
18. KAHN, R. L.: The quantitative Kahn reaction, *Ven. Dis. Inform.*, 1939, xx, 255.
19. CROSBY, E. L., JR., and CAMPBELL, A. M.: The quantitatively titrated serologic test in early syphilis and its response to treatment, *Am. Jr. Syph., Gonorr., and Ven. Dis.*, 1941. (In press.)
20. KEMP, J. E., CHESNEY, A. M., and POOLE, O. K.: The Wassermann test in normal and syphilitic rabbits, *Bull. Johns Hopkins Hosp.*, 1926, xxxix, 132.
21. MOORE, J. E., and KEMP, J. E.: The Wassermann reaction in treated early syphilis, *Bull. Johns Hopkins Hosp.*, 1926, xxxix, 36.
22. MOORE, J. E., HARDY, S. M., ROBINSON, H. M., and EAGLE, H.: The response of the quantitatively titrated Wassermann test in early syphilis to treatment with five different arsenical drugs, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1926, xx, 503.

THE CAUSES OF SECONDARY FEVER IN SULFAPYRIDINE-TREATED PNEUMONIA *

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THE beneficial effect of sulfapyridine on the course and outcome of most cases of pneumococcus pneumonia has now been definitely established. A more or less rapid drop in temperature, followed by gradual disappearance of toxicity, may be expected. The temperature usually remains at normal or nearly normal levels, and the patient recovers completely. In a small but definite group of cases, however, the temperature rises again, with the accompaniment of some degree of toxicity. In our experience such a phenomenon is more frequent in sulfapyridine-treated patients than in patients recovering spontaneously or after treatment with specific serum. When such a second rise in temperature occurs, the clinician is usually faced with the task of deciding whether the patient: (1) has developed some toxic manifestation of the drug, (2) has had a relapse, (3) has experienced a recurrence of the pneumonia, or (4) is suffering from some complication inherent in the disease itself. The decision is by no means an academic one, since it is directly concerned with treatment. In the first instance, cessation of the sulfapyridine therapy is considered a wise course; in the second, on the other hand, more vigorous treatment is often imperative; while in the third and fourth instances, the treatment might vary widely, depending upon the nature and course of the disease present.

In an attempt to find answers to such situations, we have reviewed the 339 cases of pneumococcus pneumonia treated by us with sulfapyridine and selected for study those cases in which the temperature fell below 100° F., stayed there for 12 hours or more, and then rose again, remaining over 101° F. for 24 hours or longer. Certain patients who received specific serum in addition to sulfapyridine had secondary pyrexia as a manifestation of serum sickness. None of these cases are included in the present study.

As shown in table 1, there were 32 cases which fulfilled the criteria set forth. In 7 cases, the fever was considered to be due to the drug itself. Three of these patients exhibited a morbilliform rash at the time of the second bout of fever: the other four showed no rash at any time. None of the patients with "drug fever" died.

Relapse of the pneumonia occurred in 15 cases. All of these patients had been given an initial dose of 4 grams of sulfapyridine by mouth, fol-

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TABLE I

Cases with Secondary Rise in Temperature after Sulfapyridine

Cause of Second Fever	Number of Cases	Percentage of All Cases Treated with Sulfapyridine	Number Died
1. Drug fever.....	7	2%	0
2. Relapse of pneumonia.....	15	4%	4
I. Cases with adequate treatment.....	(7)		(4)
II. Cases with inadequate treatment.....	(4)		(0)
III. Cases with doubtful treatment.....	(4)		(0)
3. Recurrence of pneumonia.....	6	2%	0
4. Complications of pneumonia.....	4	1%	2
Total cases with second fever.....	32	9.4%	6
Total cases treated with sulfapyridine.....	339	100%	—

lowed by 1 gram every 4 hours until the temperature had been normal for several days, excepting a few patients treated early in the series, who received only 2 grams as an initial dose. Some extremely ill patients received in addition 3.8 grams of sodium sulfapyridine intravenously at the beginning of their treatment and at intervals later in the course of therapy. In spite of this nearly uniform dosage, the levels of free sulfapyridine in the blood varied widely, a fact which has been noted by all investigators. We have, accordingly, subdivided the cases of relapse as follows: (1) cases in which high blood sulfapyridine levels were maintained (these patients are considered to have been adequately treated with sulfapyridine); (2) cases where the levels were consistently low (these patients are classified as inadequately treated); and (3) cases treated early in the series before blood sulfapyridine determinations were made (the adequacy of treatment in these patients is doubtful).

Seven patients had a relapse of pneumonia in spite of adequate treatment. Four, or 57 per cent, of these patients died. Four patients had a relapse after inadequate treatment, and four after treatment of doubtful adequacy. None of the patients in these latter groups died.

A recurrence of pneumonia after the patient had recovered completely from the first attack occurred in six patients. All of these patients survived the second attack of pneumonia.

Four patients had secondary pyrexia as a symptom of one of the complications of the pneumonia itself. Among these patients, two died.

CASES WITH DRUG FEVER

Each of these groups is considered separately in tables 2 to 5. Table 2 shows the patients who had "drug fever." The diagnosis was made in Cases 2, 5 and 7 by the concomitant presence of a morbilliform rash which lasted for the duration of the fever. In the other four cases, the diagnosis was based on the presence of a moderately high temperature, without marked

TABLE II
Cases with Drug Fever

No.	Age	Pneumo- coccus Type	Blood Cul- ture	Number of Lobes	Time from Start of Treatment until Temperature Below 100° F.	Time Tem- pera- ture Below 100° F.	Second Fever				Mean Blood Sulfapyridine (mg./100 c.c.)
							Duration	Height	Leuko- cytosis	Rash	
1	62	I	I	1	(days) 2	3½	3	102.2	Slight	No	7.3
2	62	III	Neg.	3	5	3	1½	101.8	No	Yes	2.9
3	14	VI	Neg.	2	½	4	3	102	Yes	No	1.9
4	23	VII	VII	1	1	2	2½	101.2	Not done	No	5.9
5	63	VIII	Not done	2	½	3	3	101.2	No	Yes	3.6
6	29	XIV	Not done	Entire right	½	2	3	103.2	No	No	Not done
7	34	XVIII	Neg.	1	1½	4½	4	104	Yes	Yes	14.8

signs of toxicity, beginning two to five days after the subsidence of the first fever, and lasting about three days, plus the absence of any other demonstrable cause for the fever. A typical case (Case 2) is illustrated in figure 1.

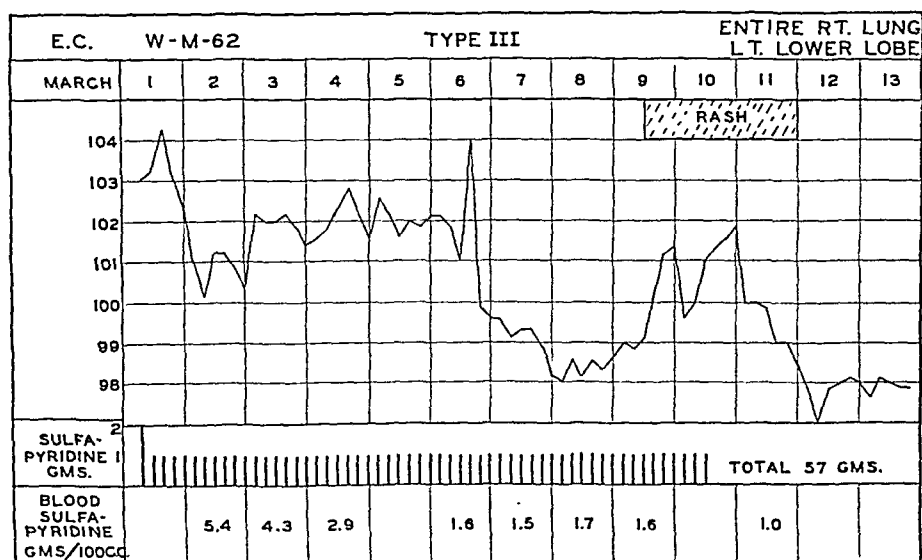


FIG. 1.

The pneumonia from which these patients suffered was varied in extent and severity. Neither the age of the patient, the number of lobes involved, nor the type of pneumococcus found in the sputum seemed to bear any relationship to the occurrence of "drug fever." The mean free blood sulfapyridine levels are given for six cases. In three patients the average level was above 5 mg. per 100 c.c., and in three patients it was below that figure. The highest average blood concentration was 14.8 mg. and the lowest 1.9 mg.

The interval between the crisis and the onset of the second temperature extended from 2 to 4½ days. The peak of the second temperature was only moderately high, except in Case 7, where the temperature rose to 104° F. This high fever, however, may be explained in part by accompanying azotemia, the blood urea nitrogen during this period having reached 100 mg. per 100 c.c.

In one case the administration of sulfapyridine had been discontinued before the fever rose, in two cases it was stopped during the course of the fever, while in four cases it was continued for a few days after the temperature had reached normal again. Regardless of the administration of the drug, the fever subsided after 1½ to 4 days.

TABLE III
Cases with Relapse of Pneumonia

No.	Age	Pneumo- coccus Type	Blood Cul- ture	Num- ber Lobes	Time Be- tween Bouts of Fever	Second Fever					Free Blood Sulfapyridine		Outcome
						Duration	Height	Leuko- cytosis	Spread	Serum Given	Mean Level	Level Before Tem- pera- ture Rise	
					(days)	(days)						mg./100 c.c.	
<i>Group I. Cases with Adequate Treatment (High Blood Sulfapyridine Concentrations)</i>													
1	24	I	I	1	½	1	104.4	Yes	No	Yes	9.8	9.4	Recovered
2	43	III	Neg.	2	3½	4½	102.4	Yes	No	No	8.5	5.9	Died
3	46	III	Neg.	3	½	7½	104.4	Yes	No	Yes	5.7	4.8	Recovered
4	37	III	Neg.	2	3	8	104.4	Not done	Yes	No	8.8	6.0	Died
5	85	III	Neg.	1	7	4	103.0	Yes	No	Yes	5.9	6.9	Died
6	38	IV	Neg.	1	1½	2	104.0	Yes	No	Yes	6.3	4.5	Recovered
7	57	XX and IV	Neg.	2	4½	39	105.0	No*	No	Yes	7.8	7.0	Died
<i>Group II. Cases with Inadequate Treatment (Low Blood Sulfapyridine Concentrations)</i>													
8	36	IV	Neg.	1	½	2½	103.4	Yes	Yes	No	2.1	2.0	Recovered
9	21	VII	Neg.	1	1	1½	103.6	Yes	No	No	2.2	2.6	Recovered
10	25	XIV	Neg.	1	1	1	103.0	Yes	No	No	3.2	2.2	Recovered
11	44	XIV	XIV	1	2	1½	102.0	Yes	No	No	0.6	0	Recovered
<i>Group III. Cases with Doubtful Treatment (Blood Sulfapyridine Concentrations Not Determined)</i>													
12	36	I	Neg.	1	1	4	106.0	No*	No	No	Not done		Recovered
13	38	I	I	1	1	2	102.6	Yes	Yes	No	Not done		Recovered
14	24	III	Neg.	2	½	7	103.2	Not done	Yes	No	Not done		Recovered
15	35	X	Neg.	1	1½	2½	103.0	Yes	No	No	Not done		Recovered

* No leukocytosis with first or second bouts of fever.

CASES WITH RELAPSE

In table 3 are shown the cases in which, after treatment with the drug, the temperature dropped and the patient seemed to be improved; but before the signs and symptoms of the pneumonia were entirely gone, the temperature rose again and the patient suffered a relapse. In Group I the average concentration of free sulfapyridine in the blood was over 5 mg. per 100 c.c. for every patient, and the concentration just before the onset of the second fever was 4.5 mg. or more. These seven patients were all severely ill, a fact which is confirmed by the following data. All of the patients were over 35 years of age except Case 1, who had another manifestation of a severe illness, namely, bacteremia. Four of the patients had a pneumococcus Type III infection, the mortality rate of which is notoriously high. Four patients had more than one lobe involved. One patient had congestive heart failure and one had uremia complicating the pneumonia from the onset.

Specific serum was administered to five of these patients after the temperature rose the second time. Two of the serum-treated patients died, as well as both of the non-serum-treated patients, making a total of four deaths among the seven patients in Group I. Figure 2 illustrates the course of the disease in a patient in this group who died (Case 4).

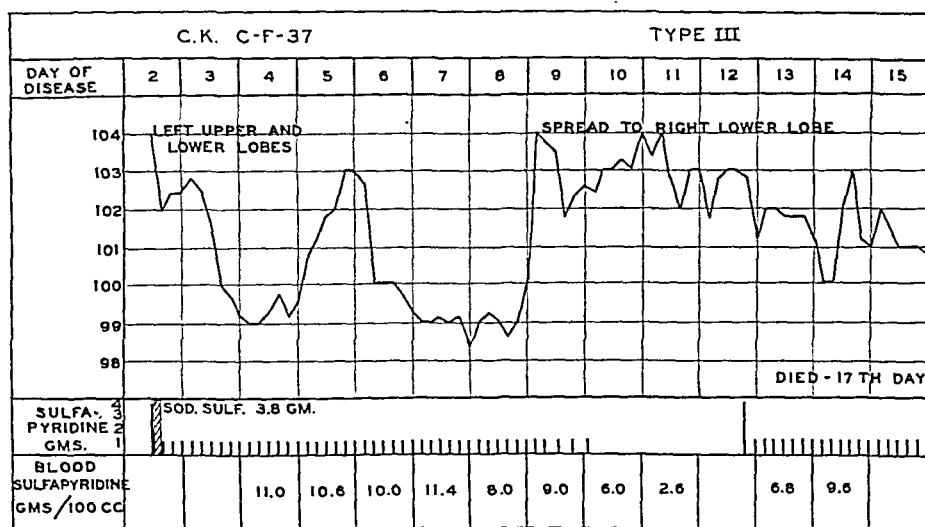


FIG. 2.

In Group II the average level of free sulfapyridine did not exceed 3.2 mg. per 100 c.c. of blood and the highest concentration in any of these patients just before the second rise in temperature was 2.6 mg. Although one of these patients (Case 11) had a bacteremia, other evidence pointed toward milder infections in this group than in Group I. The pneumococci causing the disease belonged to types above III, and no patient had more than one lobe involved. No complications were present in any of the cases. All of the patients recovered.

Group III includes those patients treated before blood sulfapyridine determinations were being done as a routine measure. It is impossible to tell whether their treatment was adequate, although one might make the assumption that they belong in the inadequately-treated group, since their infections were mild and none of them died.

Certain observations may be made regarding the entire group of patients with relapse. The peaks of the second temperature-curves were higher in general than those in the group with drug fever. All of the patients in whom the white blood cells were counted after the occurrence of the relapse showed a leukocytosis, with the exception of two (Cases 7 and 12), and these patients did not exhibit a leukocytosis at any time during the first or second bouts of fever. Signs of a spread of the pneumonia coincidentally with the second temperature elevation were present in four cases. In two of these cases, the spread occurred in adjacent lobes of the same lung, while in the other two cases the infection travelled to the other lung. The second rise in fever occurred anywhere from 2 to 6½ days after treatment with sulfapyridine was begun. In Case 4 the temperature fell and the patient was much improved after the simultaneous administration of Type III antipneumococcus serum and sulfapyridine. After three days she suddenly became worse, signs of pneumonia were present in another lobe, and she died after eight days in spite of the maintenance of high concentrations of sulfapyridine in the blood.

Sulfapyridine administration in Case 13 was discontinued one morning and that evening the temperature rose and signs of a spread were evident. Although no further sulfapyridine was administered, the patient's temperature reached normal within two days and he recovered completely. The same sequence of events occurred in Case 14. This patient also recovered from the infection in the new lobe, although no further sulfapyridine was given. The spread of the pneumonia in Case 8 (figure 3), however, occurred while the patient was on full dosage of the drug (at the rate of six grams per day). The free blood sulfapyridine had dropped from 5 mg. per 100 c.c. two days before and 3.4 mg. 24 hours before, to 2 mg. on the day of the spread. The next morning, when the temperature was at its height, the free blood sulfapyridine was 0.8 mg. per 100 c.c. Even with an injection of 3.8 grams of sulfapyridine in addition to the oral dosage, the blood sulfapyridine could not be kept at a consistently high level. Nevertheless, the fever subsided after 2½ days and the patient recovered.

CASES WITH RECURRENCE

Table 4 portrays a most interesting group of cases. We found in our series six patients who, after recovering from one attack of pneumonia while under treatment with sulfapyridine, came down with a second attack of pneumonia, caused by a pneumococcus of a different type. To this group we have added another (Case 7), an infant of eight months, seen in con-

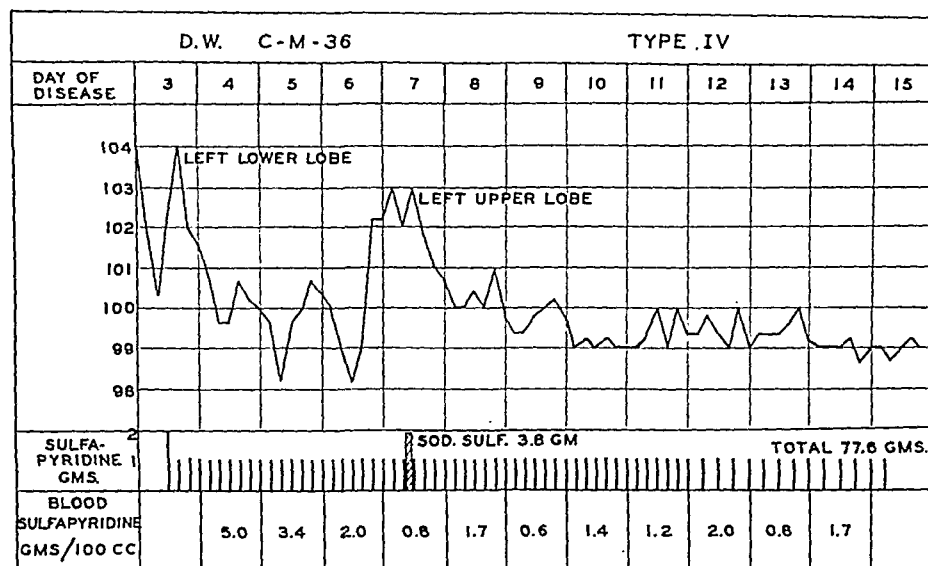


FIG. 3.

TABLE IV
Cases with Recurrence of Pneumonia

No.	Age	First Infection					Second Infection					
		Pneumo-coccus Type	Blood Culture	Lobes Involved	Treatment	Time Between Infections (days)	Pneumo-coccus Type	Blood Culture	Lobes Involved	Leuko-cytosis	Treatment	Results
1	39	III	Neg.	RM, RL	Sulfapyridine and serum	10	VIII	Neg.	LL	Yes	Sulfapyridine and serum	Recovered
2	35	IV	Neg.	LL	Sulfapyridine and serum	25	I	Neg.	LL	No*	Sulfapyridine	Recovered
3	58	XVII	XVII	LL	Sulfapyridine and serum	22	VII	VII	LU	Yes	Sulfapyridine	Recovered
4	34	XVIII	Neg.	RL	Sulfapyridine	14	XXIV	Neg.	RM	Not done	None	Recovered
5	50	XXVII	Neg.	LL	Sulfapyridine	13	VIII	Neg.	RL	Not done	None	Recovered
6	29	XXIX, XIX	Neg.	LL	Sulfapyridine	9	XI	Neg.	LL	Not done	Sulfapyridine	Recovered
7	8 mos.	VI	Not done	RU	Sulfapyridine	17	XIV	Neg.	LU	Yes	Sulfapyridine	Recovered

* No leukocytosis with first or second infection.

sultation at Children's Hospital. Because the patients were well from the first pneumonia before the onset of the second attack, we have designated these as cases of recurrence of pneumonia. The administration of sulfapyridine had been stopped for an interval of eight or more days before the second infection began in every case.

One patient (Case 3, figure 4) had bacteremia during each attack of pneumonia. During the first attack, Type XVII pneumococci were found in blood and sputum; and during the second, Type VII pneumococci in both. All of the other patients had negative blood cultures during the first and second infections, except for Case 7, in whom a blood culture was not obtained during the first attack.

F.W.		C-M-58		TYPES XVII AND VII																																				LEFT LOWER LOBE							
DAY OF DISEASE		6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46					
SPUTUM		TYPE XVII																																				TYPE VII									
BLOOD CULTURE		TYPE XVII																																				TYPE VII									
SULFA-PYRIDINE GMS.		4.9		SOD. SULF. 3.4 GM																																		SOD. SULF. 5.8 GM									
BLOOD SULFAPYRIDINE GMS/100 CC		4.9																																				4.5 5.1 4.8 3.8 1.0									

Serum was administered in addition to sulfapyridine to control the first infection in Cases 1 and 2, and during the second infection in Case 1. The remaining patients received sulfapyridine alone during both infections, except Cases 4 and 5, who were given only symptomatic treatment during the second pneumonia. All of the patients recovered.

No.	Age	Pneumo- coccus Type	Blood Cul- ture	Num- ber of Lobes	Time from Start of Treatment until Tem- perature Below 100° F.	Time Tem- pera- ture Below 100° F.	Second Fever			Complication	Outcome
							Duration	Height	Leuko- cytosis		
1	64	I	I	1	(days) 1½	(days) 3½	7	104.4	Yes	Empyema	Died
2	36	V	Neg.	1	1½	1½	7	103	Yes	Empyema	Died
3	81	XIV	Neg.	3	½	5	2	102.8	Yes	Infected sub- maxillary gland	Recovered
4	14	XIV	Neg.	1	1	1½	7	103	Not done	Massive pleural effusion	Recovered

CASES WITH COMPLICATIONS OF PNEUMONIA

In table 5 are shown those patients whose second temperature rise was due to one of the complications inherent in the disease itself. In two cases empyema developed, both patients dying as a result of this complication. One patient developed an infected submaxillary gland, and the fourth a massive sterile pleural effusion. Both recovered.

DISCUSSION

The occurrence of a febrile reaction following treatment with drugs of the sulfonamide group has been noted by many investigators. Hageman and Blake¹ reported 21 cases of "drug fever" among 134 patients treated with sulfanilamide. A rash accompanied the febrile reaction in nine cases. The reaction appeared between the fourth and thirteenth days after the institution of the fever therapy. The average duration of the fever was two to four days. The temperature usually showed only a moderate elevation. In 14 of the 21 cases it did not go above 103° F. In three of the seven cases in which the fever was higher, other complications were present which contributed to the elevation. The authors were unable to explain the mechanism of the reaction.

Brown and his associates² compared the toxic manifestations following the use of sulfanilamide and sulfapyridine. They found 14 cases of drug fever among 100 patients treated with sulfanilamide and eight cases among 100 patients treated with sulfapyridine. Six of the cases occurred among the 60 patients who received more than 25 grams of sulfapyridine, whereas two patients developed drug fever among the 40 who received less than 25 grams. Likewise, six cases occurred among 55 patients whose average free blood sulfapyridine levels were above 8 mg. per 100 c.c., as compared with two cases among 45 patients whose average levels were below that figure. The administration of larger total amounts of sulfapyridine, or the attainment of higher blood concentrations, would therefore seem to increase the frequency of this type of pyrexia.

In our series of 339 patients treated with sulfapyridine, there were only seven whose secondary bout of fever could unquestionably be called "drug fever." A number of other patients exhibited a rash, but since it occurred without fever or during the course of fever due to other causes, those cases were not included in this group. Our patients with drug fever, like those reported by Hageman and Blake, had fever of only moderate degree, which lasted from 1½ to 4 days. Three of our patients had average blood sulfapyridine levels above 5 mg. per 100 c.c., and three had average levels below this figure.

It is the usual practice to discontinue sulfapyridine when drug fever is diagnosed. While this is probably the wisest course, it does not seem to be absolutely necessary, since in four of our seven cases the temperature dropped,

the rash disappeared (if it was present), and the patient recovered, even though the drug had been continued on through the second bout of fever. In the other three cases, the sulfapyridine had been stopped before the rash appeared, or was stopped as soon as the rash was observed.

Cases of relapse apparently may occur as a result of an insufficient concentration of sulfapyridine in the blood, or as a result of an unusually severe infection which progresses regardless of the sulfapyridine concentration. If low levels of free blood sulfapyridine are found, they should be raised rapidly by means of intravenous injections of sodium sulfapyridine to supplement the oral dosage. If the levels are found to be high already, specific serum should be used. It should be given promptly and in large doses, since it is in this group of cases that serum exhibits its greatest value as an adjunct to sulfapyridine. In our group of cases suffering from relapse in spite of adequate sulfapyridine levels, three patients of the five who received specific serum recovered, while both of those who did not receive it died.

The most interesting group of cases revealed by this study are those in which a second pneumonia, caused by another type of pneumococcus, occurred. Finland and Winkler³ made an extensive study of recurrences of pneumonia. They pointed out that such recurrences are relatively infrequent, since they found only 57 instances among more than 5,000 "typed" cases. Only eight of the recurrences in this group occurred within three months of the original infection. Two of these eight patients received specific serum in the original infection, both for a Type I pneumococcus pneumonia. In both cases the second attack of pneumonia was caused by the Type I organism, the interval between attacks being one month in one case and one and one-half months in the other. This would indicate that recurrence of pneumonia after serum therapy is very seldom encountered. From our own experience we would agree with this. We have not found a single case of recurrence among 120 patients with pneumococcus pneumonia treated with specific serum alone, nor among 65 patients who were given only symptomatic treatment. In contrast to this has been our finding of six cases among 339 patients treated with sulfapyridine, all of which occurred after an interval of less than a month.

Hamburger and Ruegsegger⁴ have reported the case of a patient with Type I pneumococcus pneumonia who was practically afebrile for 14 days and was about to be discharged when he was seized with another attack of pneumonia caused by the same organism but in a different lobe. Finland, Spring and Lowell⁵ mention a patient with Type III pneumococcus pneumonia who had a recurrence six months after the first attack, which had entirely disappeared at the onset of the second infection.

Kneeland and Mulliken,⁶ after a study of the antibodies developing in 19 patients with pneumonia treated with sulfapyridine, found an excess of antibodies by means of the precipitin test in only four cases, and in these they developed after one week of normal temperature. They conclude that

"sulfapyridine has supplanted, at least to some degree, this part of the immune mechanism," that is, the production of humoral antibodies.

On the other hand, Wood and Long,⁷ using the mouse protection test in a similar study, came to the conclusion that the immune response was in no way altered by sulfapyridine treatment, and that the antibody response was much the same as that observed in untreated patients during the natural course of the disease. The complete study by Finland and his associates,⁵ making use of several different tests to study antibody titers, both before and after treatment with sulfapyridine, is in agreement with the findings of Wood and Long. It seems unlikely, therefore, that sulfapyridine interferes with the development of humoral antibodies sufficiently to permit a recurrence of pneumonia. Furthermore, in the group of seven cases which we studied, sulfapyridine had been discontinued in all except one case when the second attack of pneumonia began.

Another possible explanation of recurrence is the failure to develop local immunity, such as the macrophage reaction described by Robertson and his co-workers. They⁸ showed that dogs were just as resistant to a second infection after recovery from one attack of pneumonia whether humoral antibodies were present or not. The one consistent finding in the dogs which had had a previous attack of pneumonia was the early appearance of a generalized macrophage reaction and a marked diminution of pneumococci in the tissues. They later described in detail the macrophage reaction present in dogs⁹ recovering from experimental pneumonia and in humans¹⁰ recovering from the natural disease. They attributed the favorable outcome to the marked phagocytic power of the macrophages. It would be interesting to see whether this macrophage reaction develops as completely in patients treated with sulfapyridine.

Diagnosis of recurrence of pneumonia is not difficult when the patient is examined at intervals and found to become free of the manifestations of the pneumonia and then to develop signs and symptoms of another attack. The sputum should be re-typed in all such cases, since a different type is usually present during the second infection.

The treatment of patients with a recurrence of pneumonia after sulfapyridine treatment, is the same as if they had not had the original attack. Four of our patients were treated with sulfapyridine alone, one with sulfapyridine and specific serum, and two received only symptomatic treatment.

While the incidence of cases with a second hyperpyrexia due to complications of pneumonia itself seems to be unusually small in the present series (four cases among 339 treated with sulfapyridine), it must be emphasized that, in most cases where such complications are present, the temperature either remains elevated, or drops only partially, never exhibiting a period in which the temperatures remain below 100° F. At the present time we are not willing to hazard the opinion that the use of sulfapyridine has decreased the incidence of the complications of the disease.

The diagnosis of such complications must be made, as always, by the consideration of the clinical course, the physical signs, roentgenograms, and such laboratory procedures as are necessary. The treatment depends upon the complication existing.

SUMMARY AND CONCLUSIONS

1. Among 339 cases of pneumococcus pneumonia treated with sulfapyridine, there was a second rise in temperature in 32 cases, or 9.4 per cent. It appears that in seven of these patients the second fever was due to the drug, in 15 it was due to relapse, in six to recurrence of pneumonia, while in four patients the fever was due to one of the complications typical of pneumonia.

2. Each group has been studied separately and the distinctive features noted, especially those which would help in the clinical differentiation.

3. In particular, the cases of recurrent pneumonia after sulfapyridine are considered to be much more frequent than among patients treated with specific serum or treated symptomatically only. The possible mechanism for this phenomenon has been discussed.

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BIBLIOGRAPHY

1. HAGEMAN, P. O., and BLAKE, F. G.: A specific febrile reaction to sulfanilamide. Drug fever, Jr. Am. Med. Assoc., 1937, cix, 642.
2. BROWN, W. H., THORNTON, W. B., and WILSON, J. S.: An evaluation of the clinical toxicity of sulfanilamide and sulfapyridine, Jr. Am. Med. Assoc., 1940, cxiv, 1605.
3. FINLAND, M., and WINKLER, A. W.: Recurrences in pneumococcus pneumonia, Am. Jr. Med. Sci., 1934, clxxxviii, 309.
4. HAMBURGER, M., and RUEGSEGER, J. M.: Early recurrence of sulfapyridine-treated Type I pneumococcal pneumonia, New England Jr. Med., 1939, cci, 445.
5. FINLAND, M., SPRING, W. C., and LOWELL, F. C.: Immunological studies on patients with pneumococcal pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 179.
6. KNEELAND, Y., and MULLIKEN, B.: Antibody formation in cases of lobar pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 307.
7. WOOD, W. B., and LONG, P. H.: Observations upon the experimental and clinical use of sulfapyridine. III. The mechanism of recovery from pneumococcal pneumonia in patients treated with sulfapyridine, ANN. INT. MED., 1939, xiii, 612.
8. COGGESHALL, L. T., and ROBERTSON, O. H.: A study of repeated attacks of experimental pneumococcus lobar pneumonia in dogs, Jr. Exper. Med., 1935, lxi, 213.
9. ROBERTSON, O. H., and LOOSLI, C. G.: A study of the macrophage reaction in the pulmonary lesions of dogs with experimental pneumococcus pneumonia, Jr. Exper. Med., 1938, lxxvii, 575.
10. ROBERTSON, O. H., and UHLEY, C. G.: Changes occurring in the macrophage system of the lungs in pneumococcus lobar pneumonia, Jr. Clin. Invest., 1936, xv, 115.

THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH SULFAPYRIDINE*

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THE purpose of this paper is to report our experience with sulfapyridine in the treatment of 123 cases of lobar pneumonia in adults during the period from January 15 to May 15, 1939. During the past year many clinical reports on the treatment of pneumonia with sulfapyridine have appeared in the literature. Generally, the mortality rate has been reduced from 25 per cent to 30 per cent to below 10 per cent. Pepper et al.¹ reported 400 cases of pneumococcic pneumonia treated with sulfapyridine with a mortality of 7 per cent. Gaisford² reported 400 cases with a mortality of 6.5 per cent. Plummer and Ensworth³ reported 270 cases with a mortality of 12.6 per cent. When those deaths occurring within the first 24 hours of hospitalization were deducted this rate fell to 8.6 per cent. Volini et al.⁴ reported 60 cases with a mortality of 3.3 per cent.

In this study the clinical diagnosis of pneumonia was established by the history and the physical examination. A roentgen-ray examination of the chest was obtained on approximately 50 per cent of the patients. This confirmed the clinical diagnosis in all patients so studied. Routine sputum examination and typing by the Neufeld capsule swelling reaction was made immediately after admission, and on all patients who failed to give a direct Neufeld reaction the sputum was inoculated into the peritoneal cavity of a mouse. The blood of all patients (but one) was cultured in buffered dextrose heart infusion broth. If sputum could not be obtained and blood culture yielded no growth in 18 to 24 hours, lung puncture was performed. The free sulfapyridine blood level was determined by the Marshall method within 24 hours after treatment was instituted and then each alternate day. Blood studies were also made each alternate day. A microscopic test for the homologous agglutinin in the blood was determined frequently in about 30 per cent of the patients.⁵ All laboratory work was repeated on those patients who failed to respond to treatment within 48 hours. Every patient was examined at least once a day.

The racial distribution of the patients observed was 94 whites and 29 negroes. There were 93 males and 30 females. The youngest patient treated was 15 years of age, the oldest 76. The average age was 40.4 years.

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With the technical assistance of Dolores Lammers, B.S.

This study was made possible through the coöperation of the members of the Northwestern University Faculty, Dept. of Medicine, at the Cook County Hospital.

The sulfapyridine was made available by Merck and Co.

The dose of sulfapyridine used throughout this study was as follows: an initial dose of 2 grams was given and repeated in four hours. A maintenance dose of 1 gram was then given every four hours, day and night, until the temperature dropped to normal and remained so for two days. This was followed by 1 gram every six hours for two more days. The average daily dose was 5 grams. The average total dose administered was 31.5 grams per patient. The largest amount of drug given to one individual was 122 grams in 22 days. In approximately the first 60 cases studied, sodium bicarbonate was administered in dosage equal to the sulfapyridine. It was then discontinued.

Table 1 summarizes both the type incidence and the mortality of all the pneumococcic pneumonias treated in this study.

TABLE I
Type Incidence and Mortality

Type	No.	Died
Type I	37	6
Type II	28	2
Type III	14	1
Type IV	5	—
Type V	1	—
Type VII	16	3
Type VIII	4	—
Type X	1	1
Type XII	1	—
Type XIV	2	—
Type XVII	1	—
Type XVIII	1	—
Type XIX	1	—
Type XX	1	—
Type XXII	1	1
Type XXIII	1	—
Type XXV	1	—
Type XXVII	1	—
Unclassified	6	—
Total	123	14

Of the 123 patients with pneumococcic pneumonia there were 18 specific types represented. Type I accounted for 37 or 30 per cent; Type II for 28 or 23 per cent; Type VII for 16 or 13 per cent and Type III for 14 or 11.5 per cent. In six patients the pneumococcus was determined as the etiological agent but could not be typed with the 32 specific sera used. These are listed as "unclassified" in table 1.

In the group of 100 patients treated with sulfapyridine alone there were nine deaths, a mortality rate of 9 per cent (table 1A). Of the nine deaths, four occurred in less than 24 hours after admission making a corrected mortality of 5.0 per cent. Three of these four had bacteremia. The blood was not cultured in the fourth who died 10 hours after admission to the hospital. Bacteremia was present in 21 patients and of these five died.

TABLE IA
Pneumonia Treated With Sulfapyridine Alone

		Bacteremia		Non-Bacteremia		Total	
		No.	Died	No.	Died	No.	Died
Type	I	8	2	23	2	31	4
Type	II	6	1	13	—	19	1
Type	III	2	1	10	—	12	1
Type	IV	—	—	5	—	5	—
Type	V	—	—	1	—	1	—
Type	VII	4	1	8	1	12	2
Type	VIII	—	—	3	—	3	—
Type	XII	—	—	1	—	1	—
Type	XIV	1	—	1	—	2	—
Type	XVII	—	—	1	—	1	—
Type	XVIII	—	—	1	—	1	—
Type	XIX	—	—	1	—	1	—
Type	XX	—	—	1	—	1	—
Type	XXII	—	—	1	1	1	1
Type	XXIII	—	—	1	—	1	—
Type	XXV	—	—	1	—	1	—
Type	XXVII	—	—	1	—	1	—
Unclassified		—	—	6	—	6	—
Total		21	5	79	4	100	9
		23.8%		5%		9%	

Three of the five deaths occurred within 24 hours of admission. The mortality rate of the non-bacteremic patients was 5 per cent.

Table 1B analyzes the 23 cases of pneumococcic pneumonia treated with both sulfapyridine and serum. Six different types were represented but Types I, II and VII were isolated in 19 of the 23 patients. Of the 23 patients treated, five died. Of the 13 non-bacteremic pneumonias none died. Bacteremia was present in 10 patients and of these five died. Of the five deaths in this group of 23 patients treated with sulfapyridine and serum, one death occurred within eight hours and another within 30 hours after treatment was instituted.

For purposes of comparison of this study there were 91 patients admitted to the same hospital during the same period, January to May 1939, who received serum treatment.⁶ The mortality in this group was 10.9 per

TABLE IB
Pneumonia Treated With Sulfapyridine and Serum

		Bacteremia		Non-Bacteremia		Total	
		No.	Died	No.	Died	No.	Died
Type	I	3	2	3	—	6	2
Type	II	4	1	5	—	9	1
Type	III	—	—	2	—	2	—
Type	VII	1	1	3	—	4	1
Type	VIII	1	—	—	—	1	—
Type	X	1	1	—	—	1	1
Total		10	5	13	—	23	5
						21.7%	

cent. Sixty-four patients were treated during the first 96 hours and five of these died. Of the 27 patients who did not receive serum until after 96 hours, five died.

As a control for both studies, sulfapyridine group and serum group, there were 89 patients admitted between January and May 1939, who received neither sulfapyridine nor serum. There were 22 deaths, a mortality of 25 per cent.

An analysis of the fatal cases is of particular value in pointing out how future failures may be avoided. The factors influencing the outcome of a pneumonia, irrespective of treatment are (1) duration of the disease before treatment, (2) age, (3) bacteremia, (4) extent of lung involvement, (5) alcoholism and (6) preëxisting and associated diseases, such as diabetes, heart disease, asthma, etc.

TABLE II
Effect of the Delay in Treatment

	24 hrs.		Sulfapyridine Alone				96 hrs.		After 96 hrs.	
	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died
Total	3	—	16	—	19	—	13	—	49	9
							51	—	49	9
			Sulfapyridine and Serum							
	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died
Total	5	—	1	—	7	1	4	1	6	3
							17	2	6	3

When sulfapyridine was started after the fifth day of the disease its efficacy was markedly decreased. Of the 55 patients in whom treatment was begun after the fifth day, 12 died. Of the 68 patients in whom treatment was begun before the fifth day only two died. This delay in treatment is probably the most important single factor in prognosis and is rarely ever controlled by the physician. Further education of the public is the only hope of giving patients adequate treatment earlier in their illness.

TABLE III
Effect of Age

Age	0-20		20-30		30-40		40-50		50-60		Over 60	
	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died	No.	Died
Bacteremia	1	—	3	1	7	—	7	2	6	3	8	4
Non-Bacteremia	10	—	19	—	28	1	14	1	10	1	10	1
Mortality	—		4.5%		3%		14.3%		25%		27%	

The next factor influencing mortality in this study was age (table 3). In the group treated with sulfapyridine alone there were 56 patients under 40 years of age with two deaths while over 40 years of age there were 44

patients with seven deaths. In the sulfapyridine and serum group there were 12 patients under 40 years of age with no deaths while over 40 years of age there were 11 patients with five deaths.

TABLE IV
Extent of Lung Involvement

	1 Lobe		2 Lobes or More	
	No.	Died	No.	Died
Sulfapyridine	67	3	33	6
Sulfapyridine and Serum	16	1	7	4
Total	83	4	40	10
		4.8%		25%

The extent of lung involvement is also of prognostic value (table 4). Of 83 patients in this study who had only one consolidated lobe there were four deaths, while of 40 patients with two lobes or more consolidated there were 10 deaths. Usually the extent of lung involvement parallels the duration of the disease before treatment is begun and is therefore controllable only through obtaining medical care earlier in the course of the illness.

Invasion of the blood stream by the pneumococcus during the course of lobar pneumonia occurred in 31 of the 123 patients in this series. When it did occur it was a serious prognostic sign as indicated by tables 1A and 1B. Of 31 patients with bacteremia there were 10 deaths while of 92 non-bacteremic patients there were only four deaths. Persisting bacteremia or bacteremia appearing late in the course of illness occurred most commonly with a spreading infection. Failure of a patient to respond within 24 hours to treatment with sulfapyridine, serum or both was commonly due to an invasion of the blood stream by the pneumococcus.

In the Cook County Hospital as in other large municipal and county hospitals alcoholism is commonly associated with lobar pneumonia (table 5). In this series of 123 patients treated with sulfapyridine 26 gave a history of being moderate to heavy drinkers. Of these 26, nine died. Of the 26 alcoholics, twelve had positive blood cultures. Eight of the 12 died. De-

TABLE V
Effect of Alcohol

	Sulfapyridine		Sulfapyridine and Serum		Total	
	No.	Died	No.	Died	No.	Died
Alcoholics						
Bacteremia	6	4	6	4	12	8
Non-Bacteremia	12	1	2	—	14	1
Total	18	5	8	4	26	9
Non-Alcoholics						
Bacteremia	15	2	4	1	19	3
Non-Bacteremia	67	2	11	—	78	2
Total	82	4	15	1	97	5

lirium tremens occurred in seven patients. Six of the seven died. Of the 14 non-bacteremic alcoholics there was one death. In the non-alcoholic group of 97 patients, nineteen showed a positive blood culture but only three of the 19 died. Two deaths occurred in the 78 non-alcoholics with negative blood cultures.

ASSOCIATED AND PREEXISTING FACTORS

Heart disease was encountered in 13 patients. Fatal cardiac failure occurred in three of these, all of whom had arteriosclerotic heart disease with auricular fibrillation. Two patients with rheumatic heart disease, one decompensated, were successfully treated. Paroxysmal auricular fibrillation was noted once and did not influence the course of the disease.

Surgical procedures had been done prior to the onset of the pneumonia in three patients. In two of the patients colostomies had been performed while the other was under treatment for a cerebral concussion. All were successfully treated.

Cirrhosis of the liver was encountered once and was complicated by ascites, jaundice, esophageal varices, anemia, alcoholism and coronary sclerosis. This patient received 8.5 grams of sulfapyridine and had a level of 5.0 mg. per cent of free sulfapyridine in his blood. Death occurred 36 hours after admission.

Asthma was present in four patients. Of these, two were 69 years of age and had positive blood cultures. Both were alcoholics and died in 8 and 30 hours of admittance respectively.

Epileptic seizures were seen in two patients but five gave a history of epilepsy. One death occurred in this group, the patient dying soon after an epileptic attack.

A positive blood Kahn test was present in four patients. All recovered.

Tuberculosis was associated with pneumonia in one patient. Type II pneumococci and tubercle bacilli were recovered from the sputum. The patient recovered.

Otitis media was observed in three patients, all with negative blood cultures. All were of the chronic type with an acute exacerbation. The etiological agent in two of the three was the streptococcus.

ANALYSIS OF THE FATAL CASES

The most common complicating factor in the 14 fatal cases was delay in treatment (table 6). In only two of these was treatment begun before the fifth day of illness. In one, treatment was begun on the third day and in the other on the fourth day of the illness. The next most frequent complicating factor was bacteremia which occurred in 10 of the 14 fatal cases. A blood culture was not obtained on one of the patients who died 10 hours after admission to the hospital. Multiple lobe involvement occurred in 10 of the 14 patients. Eight of the nine alcoholics who died were bacteremic.

The complicating factors (represented in table 6 by abbreviations explained in the footnote) were much greater in the alcoholics than in the non-alcoholics. So also, was the extent of lung involvement and the bacteremic incidence. As has been pointed out by Capps⁷ and Pickerell⁸ alcohol, volatile and fixed anesthetics tie up the bodies' forces of resistance permitting infection to invade and spread.

TABLE VI
Analysis of the Fatal Cases

Patient	Age	Blood Culture	Lobes	Complicating Factors*	Duration of Illness before Treatment
J.B.	34	negative	1	AL.—CIR. J.—AN. H.D.—D.	5 days
G.N.	29	positive	2	AL.—D.—B.	5 days
T.M.	60	positive	2	AL.—B.	5 days
E.K.	65	positive	3	AL.—B.—D.	5 days
J.D.	56	positive	1	AL.—B.—D.	5 days
M.N.	49	positive	4	AL.—D.—B. L.—AN.	4 days
A.H.	69	positive	2	AL.—B.—H.D.	7 days
W.M.	69	positive	2	AL.—B.—H.D.	5 days
F.G.	40	positive	3	AL.—B.—D.—H.D.	3 days
W.H.	52	positive	2	B.—P.E.—H.D.—AN.	5 days
S.D.	44	not obtained	1	AL.	5 days
M.U.	65	negative	2	H.D.	5 days
F.J.	52	positive	1	B.—Hem.	6 days
M.M.	50	negative	1	EP.	5 days
Average	52.2	10/14—70%	2		5 days

* H.D.—Heart disease. AL.—Alcoholism. B.—Bacteremia. J.—Jaundice. EP.—Epilepsy. CIR.—Cirrhosis. P.E.—Pleural effusion. D.—Delirium. AN.—Anemia. L.—Leukopenia. Hem.—Hemiplegia.

EFFECT OF SULFAPYRIDINE ON THE CLINICAL FINDINGS

After 12 to 36 hours of sulfapyridine therapy a precipitous drop in the temperature usually occurred. This happened in the presence of bacteremia, in spite of low leukocyte counts and in the absence of the homologous agglutinins in the blood. Associated with the drop in temperature there was a drop in the pulse rate, the respiratory rate became slower and the signs of toxicity abated. Although the improvement in the general condition of the patient was quite marked, very little change in the physical signs over the involved lung could be detected for 48 hours or more. The lung remained consolidated and seemed to undergo the changes seen in an untreated pneumonia. The agglutinins did not appear in the circulating blood until the patient manifested signs of overcoming the pneumonia. Sulfapyridine therapy apparently did not affect their production. In certain patients, treated within the first 24 hours, frank signs of consolidation never did appear and the signs of infection were gone within a week. With a favorable response to sulfapyridine treatment the need for oxygen and other supportive measures was decidedly lessened.

EFFECT OF SULFAPYRIDINE ON COMPLICATIONS

Bacteremia occurred in 31 patients. Persistent bacteremia in spite of active sulfapyridine treatment was observed in two patients. One patient had five positive blood cultures during 15 days of sulfapyridine therapy during which time the amount of free sulfapyridine in the blood varied from 4.0 mg. per cent to 7.8 mg. per cent with an average of 5.6 mg. per cent. This patient died on the fifteenth day after treatment had been begun. Another patient had four positive blood cultures in succession over a period of 11 days during which time the amount of free sulfapyridine in the blood ranged from 1.25 mg. per cent to 5.25 mg. per cent with an average of 2.8 mg. per cent. A negative blood culture was obtained on the thirteenth day of treatment. This patient developed an empyema but eventually recovered.

Empyema was observed in four patients and the type pneumococcus isolated from the pus corresponded to the type pneumococcus found in the sputum. All four patients had positive blood cultures. The types represented were Type I, Type II (twice) and Type III. With continued sulfapyridine treatment and repeated chest aspirations the septic course was lessened but all four eventually required surgical drainage. All recovered.

Sterile pleural effusions occurred in eight patients, three with positive blood cultures and five with negative blood cultures. The response to continued sulfapyridine treatment and repeated chest aspirations was favorable in all patients. Repeated studies on the pleural fluid aspirated failed to yield any organism.

Delayed resolution was seen in nine patients, six with bacteremia and three without. All were confirmed by roentgen-ray. Clinically, two of these patients appeared entirely well but the others developed a fever of from 101 to 103° F. which persisted for several days and subsided gradually and spontaneously. The rise in temperature often followed an afebrile period of from 2 to 4 days.

Other complications which occurred were acute arthritis once, acute parotitis once, pronounced hypochromic anemia three times and jaundice once.

CONCENTRATION OF FREE SULFAPYRIDINE IN THE BLOOD

With the dosage used, an average level of from 4 to 6 mg. per cent of free sulfapyridine was maintained in the blood. The highest level obtained was 15.0 mg. per cent, the lowest 1.0 mg. per cent. Although it seemed desirable to obtain a blood level of 4 to 6 mg. per cent a good therapeutic response was noted with levels as low as 1.0 to 3.0 mg. per cent. No definite correlation could be made between the free blood sulfapyridine level and the clinical response.

SULFAPYRIDINE REACTIONS

As reported by others we encountered sulfapyridine reactions (table 7). The following occurred:

Gastrointestinal Symptoms. Nausea, vomiting and anorexia were the most common symptoms seen during sulfapyridine treatment but were seldom severe enough to warrant cessation of the drug. Nausea was present in 47 patients, vomiting in 25. In five patients, however, the vomiting was of such a degree that the drug was stopped. In about 50 per cent of the patients sodium bicarbonate was given and there seemed to be little effect on the prevention of the above gastrointestinal symptoms. The absorption of sulfapyridine, as evidenced by the sulfapyridine blood levels, remained essentially the same as when sulfapyridine was taken orally without sodium bicarbonate. The administration of oxygen has been used successfully in the control of nausea and vomiting due to sulfapyridine.⁹ In our study, however, these symptoms persisted in spite of oxygen administration. The number of patients observed is too small to be of significance.

Cyanosis. This developed in 12 patients and did not seem to bear any relationship to the degree of therapy. Until spectroscopic studies of the blood, and blood oxygen studies are made this sign may be questioned since cyanosis is part of the pneumonic picture.

Fever and Rash. One of the most distressing sulfapyridine reactions encountered was fever. In five patients a sulfapyridine fever was diagnosed. The fever usually occurred after 5 to 7 days of treatment, often after an afebrile period when the patient appeared clinically well. The duration of the fever varied from two to four days and ranged from 101 to 103° F. In two patients the fever developed when sulfapyridine was resumed after an interruption of two to three days which followed the initial course of several days. In all patients that showed fever and one that did not, a maculo-papular morbilliform rash appeared over the torso, arms, hands, legs and occasionally on the mucous membranes of the palate, tongue and pharynx. Both the fever and the rash disappeared after the drug was stopped.

Anemia. An acute anemia developed in one patient who had received 35 grams of sulfapyridine. Jaundice was noted. Clinically, this patient presented the picture of an hemolytic anemia but blood studies failed to corroborate this contention. Recovery occurred after stopping the drug and giving multiple blood transfusions.

Leukopenia. Although no fatal granulocytopenias developed, in four patients an initial high leukocyte count (12,000 or more) fell below 4000. One fell to 1600 and another to 1900. All recovered when the drug was stopped. In three cases with an initial low leukocyte count (below 4000) a leukocytosis developed with the administration of the drug. An initial leukopenia was not a contraindication to sulfapyridine therapy.

Cerebral Manifestations. An occasional patient showed symptoms of lassitude and headache which could be traced directly to sulfapyridine administration.

Other Toxic Manifestations. We observed one patient who developed a nitrogen retention, one an unexplained hematuria with abdominal pain and

one a severe diarrhea. All recovered and the symptoms subsided when the drug was stopped.

TABLE VII
Sulfapyridine Reactions (123 patients)

Nausea.....	49
Vomiting.....	25
Cyanosis.....	12
Fever.....	5
Skin eruption.....	6
Leukopenia (below 4000 w.b.c./cu. mm.).....	4
Anemia.....	4
Diarrhea.....	1
Hematuria.....	1
Nitrogen retention.....	1

SUMMARY AND DISCUSSION

During a period of four months, January 15 to May 15, 1939, 123 patients with pneumococcic pneumonia were treated with sulfapyridine. Mortality was 11.4 per cent. In a group of patients who received neither sulfapyridine nor anti-pneumococcus serum, mortality was 25 per cent.

Analysis of the 123 treated patients shows that sulfapyridine was effective against all types of pneumococci encountered (18 types) and that its use was relatively safe. No deaths could be attributed to sulfapyridine treatment. Nausea and vomiting occurred frequently (35 per cent) but was serious enough to necessitate discontinuation of treatment in only 4 per cent.

A study of the fatal cases indicates that the most important factor in prognosis was delay in treatment. Next in order of importance were age, extent of lung involvement, bacteremia and alcoholism. During most of this study serum was not administered until it appeared obvious that sulfapyridine alone was inadequate as indicated by the continued fever and prostration, persistent bacteremia and spread of the pneumonia to other lobes. Toward the end of the study, however, it was felt that under certain conditions serum should be given at once. These conditions were duration of the pneumonia of four days or more, age over 40, involvement of more than one lobe, alcoholism and evidence of beginning septic complications or the presence of associated diseases such as diabetes, heart disease, etc. When serum was used the initial dose was 200,000 units or more, larger doses being given when more than one of the above mentioned factors were present. Repeated administration of serum was dependent on the appearance of the patient and on the presence or absence of agglutinins in the patient's blood. We now also feel that whether any of the above mentioned factors are present or not, patients whose admission blood culture is positive should be given serum unless there has been striking improvement to sulfapyridine in the short interval elapsing from the time the blood is drawn for culture to the time the positive blood culture is observed.

While there will continue to be a small number of fatal cases, the goal should be to lower this "irreducible minimum" to below 5 per cent. This probably can be achieved through the persistent application of the principles of treatment outlined above.

BIBLIOGRAPHY

1. PEPPER, D. S., FLIPPIN, H. F., SCHWARTZ, L., and LOCKWOOD, J. S.: The results of sulfapyridine therapy in 400 cases of typed pneumococcic pneumonia, *Am. Jr. Med. Sci.*, 1939, cxcviii, 22-25.
2. GAISFORD, W. F.: Results of the treatment of 400 cases of lobar pneumonia with M and B 693, *Proc. Roy. Soc. Med.*, 1939, xxxiii, 1070-1076.
3. PLUMMER, N., and ENSWORTH, H. K.: Sulfapyridine in the treatment of pneumonia, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1847-1854.
4. VOLINI, I. F., LEVITT, R., and CAMPIONE, N. L.: Serum and drugs re pneumonia, *Ill. Med. Jr.*, 1939, lxxvi, 420-424.
5. FOX, W. W., ROSI, RENO, and WINTERS, W. L.: The Sabin agglutination test and the polysaccharide skin test (Francis) as indices of recovery in pneumonia, *Am. Jr. Med. Sci.*, 1940, cc, 649-655.
6. Data to be published by Dr. Frank Kelly.
7. CAPPS, J. A., and COLEMAN, G. H.: Influence of alcohol on prognosis of pneumonia in the Cook County Hospital, *Jr. Am. Med. Assoc.*, 1923, lxxx, 750-752.
8. PICKERELL, K. L.: Effect of alcoholic intoxication and ether anesthesia on resistance to pneumococcic infection, *Bull. Johns Hopkins Hosp.*, 1938, lxiii, 238-260.
9. WHITEHEAD, W. M., and CARTER, C. C.: Sulfapyridine in pneumonia, *Jr. Am. Med. Assoc.*, 1939, cxii, 2594-2595.

ACQUIRED HEMOLYTIC ICTERUS *

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HEMOLYTIC icterus, in its literal sense, is a term so broad and inclusive that it may embrace a wide variety of conditions in which there is hemolysis of the erythrocytes and anemia. By common usage the term is applied to a more specific entity characterized not only by increased hemolysis and anemia, but by splenomegaly, increased fragility of the erythrocytes and evidences of bone marrow stimulation. This disease has been subdivided into the familial or congenital (Chauffard-Minkowski) type and the acquired (Hayem-Widal) type. The former represents a definite, clear-cut, clinical entity, whereas there is a diversity of opinion as to whether or not the acquired form should be so recognized. There are many who feel the term "acquired hemolytic icterus" should be eliminated, believing that all such cases are in reality manifestations of the familial or congenital form, and that there is a latent, inherent tendency of the erythrocytes in these individuals to hemolyze, requiring only some infectious, toxic, or metabolic disturbance to bring this to light.^{1, 2} A diagnosis of acquired hemolytic icterus has been made in many cases only to find on further investigation that mild and heretofore unrecognized symptoms of the disease have been present in other members of the family, or to have siblings who previously had shown no evidence of the disease subsequently develop typical hemolytic icterus. Undoubtedly most cases of primary hemolytic icterus are of the familial or congenital type.

Thompson³ has divided hemolytic icterus into "typical" and "atypical" forms. The typical cases include those of the familial or congenital type together with those showing the characteristic findings of increased fragility, microcytosis, and splenomegaly regardless of whether or not a familial tendency can be detected. The "atypical" form embraces a rather heterogeneous group of conditions with acholuric jaundice. Watson⁴ has separated his cases into microcytic and macrocytic types. The microcytic group embraces the familial or congenital type, whereas the macrocytic group includes the secondary or acquired cases. It is interesting to note that all of his cases of the acquired macrocytic variety were associated with other diseases and none was idiopathic.

The clinical features of acquired hemolytic icterus are reputedly similar to those of the familial or congenital type with certain minor variations.^{5, 6, 7, 8} The clinical picture commonly accepted as being typical is as follows. The disease usually makes its appearance after puberty, most frequently in early adult life, but occasionally in childhood. The onset may be gradual or it may be sudden with pain in the left upper quadrant, or with a rapidly de-

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veloping jaundice, anemia, fever, and prostration. A sudden onset is reported to be more common in the acquired than in the familial form, and the "crises of deglobulization" more frequent and more severe. The spleen is usually enlarged, but the size varies from time to time and tends to increase in size with the severity of the hemolytic crises. The anemia varies in its severity and erythrocyte counts below one million are common. The color index remains at about one. The reticulocytes are increased to a variable degree. An increased fragility of the erythrocytes is usually present but frequently this is not as marked as in the familial form and there are many cases in which the fragility is within normal limits. The presence in the blood of autoagglutinins has been reported but is not specific for this disease.^{5, 8, 9} The course is frequently more rapid than in the familial form and there is a tendency for the condition to become worse with advancing age. The principal differences in the clinical course that supposedly distinguish the acquired from the familial form are the onset in later life, a more rapid course, less marked or a complete absence of changes in the fragility of the erythrocytes, and a smaller percentage of reticulocytes. The acquired form has been subdivided into two groups, those which are idiopathic in origin and those which are secondary to other diseases. In the latter group, acquired hemolytic icterus has been found associated with syphilis, malaria, tuberculosis, ischio-rectal abscess, septicemia, and other infections, as well as with leukemia, cirrhosis of the liver, and pregnancy.⁸

We have preferred to retain the term acquired hemolytic icterus and have collected from the records of the University Hospital 13 such cases. An analysis of these corroborates some of the features which have been considered as characteristic but does not substantiate others. The significant points in the findings and history of these patients are given in table 1.

TABLE I

Case	Age	Sex	Etiology	Hb. Grams	RBC Mil- lions	WBC	He- mato- crit	Color In- dex	Vol. In- dex	Sat. In- dex	Fragility	Re- ticu- lo- cytes	Jaun- dice	Spleen
1	25	F	Pregnant	7			26		.8		.50-.38	2	+	-
2	32	F	"	4.9	3.10	10,000	23.5	.54	.88	.61	.50-.36	4.5	+	-
3	40	F	"	4	2.77	11,200	19	.51	.80	.63	.56-.44	7	-	+
4	20	F	"	2.9	0.85	7,200	11.5	1.23	1.47	.84	.48-.34	27.5	+	+
5	28	F	Bronchi- ectasis	7.1	2.92	9,700	20	.84	.79	1.06	.60-.42	2.4	+	+
6	20	F	Flu	2.1	0.81	18,100	6.5	.93	.93	1.0	.60-.34	15.8	+	+
7	14	F	None	5.5	1.23	12,500		1.5			.46-.40	26.4	+	+
8	49	F	Ca. of lip	2.2	1.51	7,500	15	.53	1.16	.45	.50-.44	3	+	+
9	66	F	None	5.2	0.97	22,000		1.8			.54-.38	6.7	+	+
10	28	F	"	12.3	4.25	6,800		1.0			.50-.44		+	+
11	52	F	"	6	2.68	5,300	24	.77	1.0	.75	.58-.44		+	+
12	69	M	"	9	3.00	18,000	30	1.05	1.16	.9	.50-.38	7.2	+	+
13	8	F	"	5.1	0.92	8,700		2.0			.48-.38	15.2	+	-

Indices calculated from the tables of OSGOOD, E. E.: Laboratory diagnosis, 1935, P. Blakiston's Son & Co., Philadelphia, ed 2, p. 421.

Fragility determinations were made by suspending the cells in varying degrees of hypotonic saline and for routine use the highest percentage of saline was 0.5 per cent. In some instances additional tubes were set up to carry the determinations above this figure. Unfortunately, in others, no additional tubes were used so that the extent of the increased fragility above 0.5 per cent was not determined in all.

In none of these patients was any family history of a similar or related condition obtained. In four, the disease was associated with pregnancy and in all of these it presented a very mild course so that no treatment for the hemolytic icterus was necessary. Case 1 was discharged from the hospital before delivery and although the manifestations of the hemolytic anemia had not completely subsided at this time, her condition was improving rapidly. In cases 2 and 3 the manifestations persisted until delivery but rapidly subsided thereafter. Case 2 had been jaundiced with each of three preceding pregnancies and the jaundice had promptly disappeared after each delivery. She had had no manifestations of the disease except during the pregnancies but it is not known whether or not the increased fragility persisted during the intervals. In case 3 there was a mild toxemia of pregnancy with albuminuria and edema but this was not present in the others and we have noted no association between toxemia of pregnancy and hemolytic icterus. In case 4 the manifestations of hemolysis and anemia appeared two weeks after a normal pregnancy and delivery and upon admission to the hospital seven weeks later the symptoms were subsiding. She still presented a marked reticulocytosis, polychromatophilia, bilirubinemia, jaundice and splenomegaly. Because of the high color index, the possibility of pernicious anemia of pregnancy was considered, but the normal gastric acidity in the presence of the other findings was more suggestive of hemolytic icterus. There was a history of a similar episode during a preceding pregnancy at which time the jaundice disappeared spontaneously after an abortion at five months. The clinical course in all of these cases was relatively benign and except for case 4 a spontaneous recovery ensued after delivery. This is in accord with other reports of hemolytic icterus in pregnancy.^{10, 11, 12}

The hematological features of these cases were not identical. The saturation index was low in all. The volume index and color index were elevated in case 4 but low in the other two on whom the determinations were made. Case 4 did not correspond to the primary anemia of pregnancy because of the increased fragility, the high reticulocytosis, and the presence of a normal gastric acidity. The other cases were hypochromic and microcytic in type and although an increased fragility has been demonstrated in certain cases of hypochromic anemia of pregnancy, this condition does not present the jaundice, bilirubinuria, and spontaneous reticulocytosis.

The importance of infection as an etiological or precipitating factor is difficult to evaluate. It may be of significance that "flu" preceded the onset in one patient, in whom the jaundice and anemia developed immediately thereafter. One case (case 5) was associated with bronchiectasis.

This patient had also been jaundiced with a preceding pregnancy, but the jaundice subsided when this was terminated. A similar reaction to both infection and pregnancy would suggest a latent hemolytic tendency appearing with various types of stimuli.

In case 8 a carcinoma of the lip without evident metastases was present but it seemed doubtful if this could be considered as the etiology. In the remaining cases no etiological factor could be ascertained. No essential differences were noted between the secondary and the idiopathic cases in respect to their acuteness or their course.

In three cases an irregular febrile reaction was present. The fever was highest in case 7 in which it reached 105 degrees. Case 6 had a rapid course with irregular spikes of temperature but following splenectomy the temperature subsided to normal. Case 8 was less acute and the febrile reaction was less marked. The course of the disease was mild in all but four cases, and in only three could the disease be said to have progressed more rapidly than is common in the familial form. Repeated episodes of jaundice were not as pronounced as is common in the familial form of the disease and recurrences were present in only four cases (cases 5, 7, 11 and 13). In this respect, our cases differ from many of the reports, in that the recurrences and the "crises of deglobulization" have not been more severe than those encountered in the familial form.

Splenectomy was performed in two cases and in both of these the immediate response was good. In one instance the fragility of the erythrocytes was definitely decreased after the operation although it did not return to normal. The operation had no effect on the fragility of the erythrocytes in the other case. Neither patient has shown any evidence of increased hemolysis following the operation, and after three and four years respectively, both are in good health.

The dangers which accompany the giving of a transfusion to patients with hemolytic icterus have been mentioned incidentally by a number of authors,^{2, 7, 13, 14, 15, 16} but specific attention has been directed to this feature by Sharpe and Davis.¹⁷ They report two cases in which transfusion reactions occurred, in neither of which was the reaction fatal. The outcome is not always so fortunate as is illustrated in the following case.

Case 7. A 14 year old white girl became pale but not jaundiced two years prior to her admission to the hospital and one year later she had a similar episode. Recovery on both occasions was satisfactory. One week before admission she became nauseated and vomited and was found to be anemic. There had been no fever, chills, hemorrhages, or purpura. There was no family history suggestive of hemolytic icterus. Examination revealed a pale, icteric girl with no lymphadenopathy but the spleen extended to the level of the umbilicus. The blood showed 5.5 gm. of hemoglobin, 1,230,000 erythrocytes, and 12,500 leukocytes with a definite shift to the left. Hemolysis of the erythrocytes began at 0.46 per cent saline and was complete at 0.40 per cent saline, representing a slight increase in the concentration at which hemolysis was complete. There were 26.4 per cent reticulocytes. The smear showed a macrocytosis and polychromasia.

It was extremely difficult to find suitable donors for blood transfusions as agglutination appeared with most of the bloods selected for cross matching. Satisfactory cross matchings were eventually obtained and she received six transfusions of apparently compatible blood. Although no immediate reaction occurred, the jaundice and anemia increased more rapidly after these were given and death occurred 10 days after the first transfusion.

At autopsy the spleen was large (730 grams), dark red in color, and the liver showed increased iron pigmentation and bile stasis. The gall-bladder contained a few calculi. The bone marrow of the mid femur was deep red in color and was hyperplastic on microscopic examination. In the spleen the sinusoids were distended with blood and evidences of erythropoiesis were present. The findings were those of increased hemolysis and erythropoiesis, and the pathological diagnosis was hemolytic icterus.

Prior to the transfusions in this patient, pallor and anemia had been the most conspicuous features, whereas after these were given, jaundice became increasingly more prominent. The erythrocyte count dropped steadily regardless of the added blood. It seemed that the administration of transfusions not only led to hemolysis of the transfused blood but also accelerated the rate of hemolysis of the patient's own blood. Anuria and uremia were not present and a careful study of the kidneys did not show pigment infarcts but as Witts¹⁸ has emphasized, hemolytic transfusion reactions may be directly fatal without leading to uremia.

A second case, almost identical to the preceding one, presented the same difficulties in finding a suitable donor and did not receive a transfusion because no satisfactory cross match could be obtained. Over 70 donors of the proper blood group (Group IV Moss, A B Landsteiner) were cross matched but none was found compatible.

Case 13. A white female, aged 8, had shown an increasing weakness for 10 days and was sent home from school by the nurse because of anemia. She was given liver extract with no benefit, and the home physician attempted to give a transfusion, but could find no blood in 21 donors which would cross match with the patient's. There was no bleeding, rash, or diarrhea. The family history was entirely negative. On admission the child was extremely pale with a slight icterus, an enlarged spleen, and a barely palpable liver. The hemoglobin was 5.1 grams, the erythrocyte count 920,000, and the leukocyte count 8,700. The differential count showed a distinct shift to the left in the granulocytic series. The smear showed a macrocytosis and polychromasia of the erythrocytes, and the fragility was slightly increased, hemolysis beginning at 0.48 per cent saline and was complete at 0.38 per cent. There was a bilirubinemia of 4.7 mg. per cent, and the Van den Bergh reaction was indirect. There were 15.2 per cent reticulocytes, and 9 nucleated erythrocytes were found per 100 leukocytes.

The patient ran an irregular febrile course in which the temperature occasionally reached 102 degrees. Her condition improved somewhat and she went home, but returned to the hospital from time to time and at the last examination the blood showed 11 gm. of hemoglobin, and 3,950,000 erythrocytes. A blood transfusion was thought advisable, but a satisfactory cross match could not be obtained, although over 50 donors were tried. A splenectomy was advised, but the patient died at home without the parents giving consent to the operative procedure.

Serological examination revealed a negative Wassermann reaction but a positive Kahn. There was no clinical evidence of syphilis in the patient nor in either of the

parents, both of whom had negative Wassermann and Kahn tests. Antisymphilitic therapy had no effect on the course of the disease and the Kahn reaction was thought to be a false positive. No difficulty was encountered in doing erythrocyte counts and no evidence of auto-agglutination was detected.

There is a possibility that these two patients may have had familial hemolytic icterus in spite of the negative family history, but certain other features are against this assumption. The course in both was more rapidly progressive than is usual in the familial form, and in both patients the anemia, rather than jaundice, was the outstanding feature. The fragility of the erythrocytes was but slightly increased. In both cases extreme difficulty was encountered in finding a suitable blood donor, and in the second case this was never accomplished. The principal objection to the diagnosis of acquired hemolytic icterus is the age of onset, but if one admits the possibility of there being an acquired form, this is not an insurmountable objection. Because of the age of the patients, the diagnosis of the acquired form of hemolytic icterus is less secure than in the other patients.

The difficulties encountered in cross matching bloods for transfusion in these two patients agree with previous reports and the end result of the transfusions in case 7 illustrates the dangers which may be encountered in this procedure, and lends some indirect evidence to the belief that hemolysins are present in the blood serum. Spherocytosis was not noted. Repeated transfusions were given to other cases in this series without reactions and with good results. In the entire group four received transfusions. In addition to the above fatal reaction, a second case (case 6) had a hemolytic reaction with deepening jaundice after a transfusion but recovered satisfactorily and a splenectomy was performed later. In the other two cases there were no untoward effects from the transfusions. These results indicate that although transfusions must be given with extreme caution to these individuals the diagnosis of acquired hemolytic icterus is not an absolute contraindication to transfusion.

The following case is presented in detail because of certain unusual features.

Case 12. A 69 year old, white male was operated upon for appendicitis 23 years before and had two subsequent operations for intestinal obstruction. He was admitted to the hospital because of jaundice and pain in the right upper quadrant of the abdomen. Roentgenograms of the stomach and colon were negative, but cholecystograms revealed a non-functioning gall-bladder. At operation the gall-bladder was normal except for massive adhesions. Postoperatively the patient became more deeply jaundiced. Prior to operation there were 14.9 gm. of hemoglobin, the erythrocytes numbered 4,300,000, and the leukocytes 9,800. Following operation a leukocytosis of 61,500 developed, with a distinct shift to the left and an occasional nucleated erythrocyte. No other evidence of infection could be found except an irregular fever which gradually subsided to normal. The jaundice disappeared, but the leukocytes were persistently above 20,000. The erythrocyte count dropped to 2,170,000 during the period of icterus. Five months later he returned to the hospital because of weakness and pain in the back. There were marked pallor and slight icterus. The spleen was not enlarged, but the liver edge was just palpable. There were 9

gm. of hemoglobin, the erythrocytes numbered 3,000,000, and there were 18,000 leukocytes. The smear showed a definite macrocytosis. Hemolysis of the erythrocytes began at 0.5 per cent saline, and was complete at 0.38 per cent saline. There was a reticulocytosis of 7.2 per cent and 5 mg. per cent bilirubinemia. A sternal biopsy showed hyperplasia of the bone marrow with a normal distribution of the various cells without overgrowth of any particular type. No evidence of leukemia could be found. During observation in the hospital the jaundice disappeared and the leukocytes dropped to 15,100. Two years later he returned to the hospital because of weakness. He had a slight degree of jaundice. The spleen was definitely enlarged at this time and the liver was 3 cm. below the right costal margin. The smear showed anisocytosis and a definite macrocytosis. The fragility was increased to 0.5 per cent saline and there were 14.4 per cent reticulocytes. The gastric juice contained a normal amount of acid. The reticulocytes were not increased by the administration of liver extract intramuscularly.

The splenomegaly, reticulocytosis, anemia, and increased fragility of the erythrocytes are in keeping with the diagnosis of hemolytic icterus. The increased leukocytic count which developed with the anemia during the post-operative period is of interest. A diagnosis of leukemia was not substantiated by the clinical or hematological features, nor by biopsy of the sternal bone marrow, and after three years of intermittent observations, no evidence of leukemia appeared. A leukocytosis is present in many cases of hemolytic icterus, but usually not to this degree in the adult.

There are many features that are common to all forms of primary hemolytic anemia and the placing of a particular case in a distinct group is often times difficult, particularly if it is slightly atypical. The acute hemolytic anemia of Lederer^{19, 20} or Brill²¹ may be almost indistinguishable from hemolytic icterus of the familial or the acquired form.²² It does not present any change in the fragility of the erythrocytes but this may be lacking in hemolytic icterus. It presents a high fever but this may be present in the crises of hemolysis in hemolytic icterus so that differentiation of the two diseases may be difficult. It is important, however, that the differentiation be made if possible inasmuch as transfusions are specific in the treatment of acute hemolytic anemia whereas they are dangerous and must be given with extreme caution in acquired hemolytic icterus.

There are many chemicals that may produce hemolysis of the erythrocytes and it is at times difficult to evaluate the part they have played in producing an anemia. The exposure to amyl acetate in the following case was very slight but it cannot be said with certainty that it was innocent. The diagnosis lies between acquired hemolytic icterus, acute hemolytic anemia (Lederer) and a secondary hemolytic anemia from chemicals. There are obvious objections to each of these and the case illustrates the difficulties encountered in the differential diagnosis of hemolytic anemias.

A white male aged 27 first noticed weakness in July 1934. One month later he was so weak that he was unable to work and shortness of breath and palpitation were prominent. It was noted at this time that he was very pale and slightly jaundiced. The weakness progressed so that in November he was confined to bed for ten days.

The symptoms persisted and in February 1935, he became so weak that he was unable to sit up. He was admitted to the hospital February 21 because of these complaints. He stated that he had occasional attacks of diarrhea lasting for two to three days and that two years previously he had had a spell of weakness and pallor similar to the present illness but of shorter duration. He had worked as a mechanic for several years and had sprayed some lacquer which contained amyl acetate. After becoming weak he stopped work but the weakness persisted for seven months after he was in any way associated with this chemical. Although it cannot be entirely disregarded, we feel that the exposure to paint in this case was not the etiological factor in producing the hemolysis.

Examination revealed the patient to be very drowsy and weak and to have a marked pallor and slight icterus. The tongue was not atrophic and the gums were not infiltrated. There was no lymphadenopathy. The pulse rate was rapid, the precordial impulse was prominent and a systolic murmur was audible. The liver edge was below the right costal margin, but the spleen was not enlarged. There were no neurological changes.

On admission the patient had 1.8 grams of hemoglobin, 1,300,000 erythrocytes and 7,750 leukocytes. A differential count showed 47 per cent segmented neutrophils, 29 per cent band neutrophils, 3 per cent myelocytes, 16 per cent lymphocytes, and 5 per cent monocytes. There were eight nucleated erythrocytes per 100 leukocytes. There was marked anisocytosis and poikilocytosis. The platelets were present in normal numbers, the fragility of the erythrocytes was normal and the clot retracted normally. The bleeding, coagulation and prothrombin times were normal. The hematocrit was 8.5 per cent and there were 5.8 per cent reticulocytes. The color index was 0.46; the volume index 0.8, and the saturation index 0.57. The gastric acidity was normal. The Van den Bergh showed 3.8 mg. per cent bilirubinemia. The Wassermann reaction was negative. The plasma proteins and blood nitrogen were normal.

He received two transfusions of 500 c.c. each, and iron and ammonium citrates, 1 gram three times a day. The hemoglobin increased to 7.8 grams and the erythrocyte count to 4,500,000. The slight continuous febrile reaction which he had at the time of admission subsided and the bilirubinemia returned to normal.

When examined six months later there were 9.6 grams of hemoglobin; the hematocrit was 36.5 per cent, and there were 4,650,000 erythrocytes.

An occasional case of pernicious anemia with somewhat atypical manifestations may at times suggest acquired hemolytic icterus. The following case presented an unusually high temperature and a very sudden onset for pernicious anemia. Liver extract had been given prior to his admission to the hospital and he entered with an elevated reticulocyte count. The most unusual feature was the persistence of the reticulocytosis at a high level for 20 days. In view of the family history it was believed that this patient had an atypical form of pernicious anemia although some features suggested an acute hemolytic anemia.

A white male, aged 26, was perfectly well until three weeks prior to his admission to the hospital. At this time he noted listlessness, lack of pep, shortness of breath on exertion, and palpitation. There had been some loss of appetite and he had lost 15 pounds in weight. The mouth had been sore at intervals for several months but there was no soreness of the rectum. Jaundice was noted by his home physician at the onset of the illness. He had noticed a chilly sensation at intervals during his illness. There was no numbness or tingling of the hands or feet. The past history was negative. The patient's father had died of pernicious anemia.

Examination revealed a marked pallor and slight icterus of the skin and sclerae. The fundi showed a typical anemic retinitis with many hemorrhages. The tongue was a deep red color but showed no evidence of atrophy. There was no lymphadenopathy. The lungs were clear. There was a systolic haemic murmur over the precordium. The spleen extended 2 cm. below the costal margin and the liver edge was just palpable.

The blood showed 4.0 grams of hemoglobin, 1,000,000 erythrocytes, and 2,500 leukocytes. A differential count showed 20 per cent neutrophils, 68 per cent lymphocytes, 6 per cent monocytes, and 6 per cent nucleated erythrocytes. There were marked anisocytosis, poikilocytosis and macrocytosis and the fragility of the erythrocytes was decreased. The platelets were diminished. The hematocrit was 14.5 per cent and there were 18.4 per cent reticulocytes. The color index was 1.4 and the volume index 1.7. The temperature at the time of admission was 105 degrees. The Van den Bergh showed 3 mg. per cent bilirubinemia with a biphasic reaction. There was a complete achlorhydria.

The patient had received liver extract intramuscularly for the two days preceding admission and he continued to receive it during his stay in the hospital. The reticulocyte response was not characteristic in view of the fact that 23 days after the institution of liver therapy there was still a reticulocytosis of 20 per cent.

The fever subsided gradually and became normal on the ninth hospital day and the laboratory evidences of thrombopenic purpura had disappeared by the thirteenth day. He was discharged after 20 days in the hospital with a hemoglobin of 9 gm., 3,670,000 erythrocytes, and 4800 leukocytes.

With the exception of the cases of familial or congenital hemolytic icterus, an accurate classification of the hemolytic anemias in the adult is extremely difficult and such cases present some of the most puzzling problems in the field of hematology. The barriers erected for the subdivision of the hemolytic anemias are arbitrary and in many instances will subsequently be found to be erroneous. We have, however, elected to retain the term acquired hemolytic icterus to accommodate certain of these cases with no evident familial tendency and with certain atypical features which are not characteristic of the familial type. It is a distinct possibility that all such cases are actually of the familial type but in the present state of our knowledge in regard to the etiology and pathological physiology it seems best to retain the term.

Certain of these cases pursue a mild course, such as those that we encountered in association with pregnancy, and in this group no specific therapy is indicated. The course was also mild in some of the idiopathic cases so that in this respect the older idea that the acquired form of hemolytic icterus pursues a more rapid and acute course than does the familial form is erroneous.

Splenectomy is advisable in certain carefully selected cases in which the disease is more severe and acute. In the two instances in this series of cases the results were extremely satisfactory, both patients were in good health when last contacted and neither had had any sign of a recurrence of the hemolysis. It is interesting to note that a definite improvement occurred in the fragility of the erythrocytes after splenectomy in one case but pro-

duced no change in the other. In retrospect it would seem advisable to have recommended splenectomy earlier in the course of cases 7 and 13.

The administration of transfusions to these patients must be undertaken with caution, realizing that severe hemolytic reactions are prone to occur with an ultimate increase in the severity of the anemia. In spite of this danger there are instances when the risk must be accepted and transfusions given, but it is doubtful if they should be attempted in those instances in which exceptional difficulty is encountered in cross matching the bloods even though an apparently satisfactory donor is eventually found. The clinical syndrome which is now recognized as acute hemolytic anemia (Lederer or Brill's anemia) presents a different problem, for in this disease transfusions are apparently curative. Although one fatal transfusion reaction has been reported in this disease,²³ the procedure does not seem to be attended by the same risk encountered in hemolytic icterus. Unfortunately the clinical and laboratory features are so similar in the two conditions that differentiation is difficult.

There was no relationship in these patients between the severity of the anemia and the degree of jaundice, and the two patients with the least jaundice had extremely low erythrocyte counts. Watson⁴ has emphasized this feature and found no correlation between the degree of jaundice and the severity of the anemia except during the hemolytic crises.

The presence of spherocytosis was not consistently present in these cases and macrocytosis was more frequently encountered.

Damesliek and Schwartz²⁴ believe that since reticulocytes are larger than normal erythrocytes, an increase in these cells may mask an underlying spherocytosis and produce a "pseudomacrocytic" anemia. Since there was no correlation between the macrocytosis and the reticulocytosis this explanation is not applicable to this group of cases.

CONCLUSIONS

Observations on a series of 13 cases of acquired hemolytic icterus are presented. Not all of these were secondary to other diseases and it is believed that idiopathic acquired hemolytic icterus should be considered separately from the familial or congenital form.

The diagnostic difficulties encountered in atypical types of hemolytic anemia are stressed and some of the unusual manifestations of acquired hemolytic icterus are emphasized.

Splenectomy is advisable in certain carefully selected cases of acquired hemolytic icterus. Transfusions must be given with caution and with the realization that hemolytic reactions are prone to occur.

The intensity of the jaundice does not parallel the severity of the anemia. The fragility of the erythrocytes is usually increased but this is not always accompanied by microcytosis or spherocytosis. A macrocytic type of anemia is frequently encountered.

BIBLIOGRAPHY

1. CHENEY, W. F., and CHENEY, G.: Chronic hereditary hemolytic jaundice, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 191-213.
2. LORD DAWSON OF PENN.: Hemolytic icterus, *Brit. Med. Jr.*, 1931, 1, 963-966.
3. THOMPSON, W. P.: Hemolytic jaundice, *Jr. Am. Med. Assoc.*, 1936, cvii, 1776-1781.
4. WATSON, C. J.: Hemolytic jaundice and macrocytic hemolytic anemia: certain observations in a series of 35 cases, *ANN. INT. MED.*, 1939, xii, 1782-1796.
5. KRUMBHAAR, E. B.: A classification and analysis of clinical types of splenomegaly accompanied by anemia, *Am. Jr. Med. Sci.*, 1915, cl, 227-245.
6. LYNCH, J. H.: Acquired hemolytic icterus, *Nebr. State Med. Jr.*, 1932, xvii, 71-75.
7. WITTS, L. J.: The pathology and treatment of anemia. III. The hemolytic anemias, *Lancet*, 1932, i, 601-605.
8. TILESTON, W.: Hemolytic jaundice, *Medicine*, 1922, i, 355-388.
9. GALLIE, W. E., and JANES, R. M.: Hemolytic jaundice associated with splenomegaly, *Canad. Med. Assoc. Jr.*, 1926, xvi, 379-383.
10. MURDOCK, T. P.: Hemolytic anemia of pregnancy with reports of cases, *ANN. INT. MED.*, 1927, i, 133-136.
11. MINOT, G. R.: Two curable cases of anemia. I. Chronic hemolytic anemia, *Med. Clin. N. Am.*, 1921, iv, 1733-1750.
12. ALLAN, WM.: Hemolytic anemia in pregnancy, *Surg., Gynec. and Obst.*, 1928, xlvii, 669-672.
13. LORD DAWSON OF PENN.: Indications for, and results of, removal of the spleen, *Brit. Med. Jr.*, 1932, ii, 699-700.
14. WISE, W. D.: Hemolytic jaundice, *Am. Jr. Surg.*, 1933, xx, 722-736.
15. DOAN, C. A., WISEMAN, B. K., and ERF, L. A.: Studies in hemolytic jaundice, *Ohio State Med. Jr.*, 1934, xxx, 493-504.
16. DUTHIE, E. S.: Acquired hemolytic jaundice, *Lancet*, 1937, i, 1167-1169.
17. SHARPE, J. C., and DAVIS, H. H.: Severe reactions following transfusion in hemolytic jaundice, *Jr. Am. Med. Assoc.*, 1938, cx, 2053-2056.
18. WITTS, L. J.: A note on blood transfusion, *Lancet*, 1929, i, 1297-1299.
19. LEDERER, M.: A form of acute hemolytic anemia probably of infectious origin, *Am. Jr. Med. Sci.*, 1925, clxx, 500-510.
20. LEDERER, M.: Three additional cases of acute hemolytic (infectious) anemia, *Am. Jr. Med. Sci.*, 1930, clxxix, 228-236.
21. BRILL, I. C.: Acute febrile anemia; a new disease?, *Arch. Int. Med.*, 1926, xxxvii, 244-247.
22. MURRAY-LYON, R. M.: Familial acholuric jaundice simulating Lederer's anemia, *Brit. Med. Jr.*, 1935, i, 50-52.
23. PAYNE, R. V.: Acute hemolytic anemia; death after transfusion, *Guy's Hosp. Rep.*, 1934, lxxxiv, 65-71.
24. DAMESHEK, W., and SCHWARTZ, S. O.: Hemolysins as the cause of clinical and experimental hemolytic anemias, *Am. Jr. Med. Sci.*, 1938, clxxxvi, 768-792.

INTRAVENOUS STREPTOCOCCIC VACCINE TREATMENT OF CHRONIC RHEUMATOID DISEASE*

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STREPTOCOCCIC vaccine and streptococcic derivatives have been used in the treatment of arthritis and rheumatoid diseases for a number of years. The materials injected have varied widely as to the strain or strains used, dosage, frequency, and route of administration.

For the past nine years intravenous streptococcic vaccine has been used by us in the treatment of patients with chronic arthritis and associated rheumatoid complaints. These were seen at the out-patient department of the University of Minnesota hospital. The chief basis for use has been the probability that streptococci may be etiological factors in many cases of chronic arthritis and other rheumatoid complaints. It is granted that the streptococcic etiology has not been proved to the satisfaction of all investigators, and it is also granted that gonococci and probably other organisms will produce an arthritic process in some instances. The contributing significance of climate, exposure, occupation, trauma, inciting infectious processes, age, sex, and the constitutional predisposition of the individual likewise cannot be ignored.

In a condition such as chronic arthritis, it is very difficult to evaluate definitely any form of therapy. The course of the disease may be characterized by periods of remission and exacerbation that are difficult to explain. The clinical activity may in some instances be transitory, subsiding in a short period of time, in others after a period of years, and in many only with death which is usually from some other cause. The seeming beneficial psychological effects of various forms of faith healing or practices closely allied, have been demonstrated by many striking procedures which have attracted large numbers of persons with rheumatoid complaints. Miraculous cures are also reported frequently after many types of internal and external medications. With these factors in mind we are submitting the evidence of our experience with intravenous streptococcic vaccine, realizing that the course of the disease, the increased rest and general care associated with any procedure, and the psychological effect, cannot be minimized as accounting for some of the improvement reported.

METHOD OF TREATMENT

Streptococcic vaccines of various strains, both single and polyvalent, have been used by us in the treatment of patients with rheumatoid manifestations. The majority, however, have received a vaccine made from a

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single strain of *Streptococcus viridans* (alpha). The series analyzed were all treated with this strain, which is of low virulence and can be safely given in large doses.

The vaccine has been given by the intravenous route in all instances. The basis for intravenous use rests on animal and human experimentation and has been previously reviewed by us.¹ The usual routine has been to give eight injections at weekly intervals beginning with 100 million heat killed organisms and increasing by 100 million each week, so that the eighth dose is usually 800 million. If clinical improvement has apparently been manifested during this period or in the four weeks following, the patient continues to receive 800 million every two to four weeks for a variable period of time, in some instances for several years or more. In many cases the maintenance dose will be larger, ranging from 1200 million to 2400 million. If improvement has not been apparent following the routine injection of eight weekly injections, a further trial has been given using larger doses at two weekly intervals such as 1,200 million, 1,600 million, 2,000 million and 2,400 million. If there is still no clinical benefit after these large doses, vaccine is discontinued as of no value. If on the other hand improvement has followed only after such large doses, these are continued at two to four week intervals and, often for several years.

CLINICAL RESULTS

A series of some four thousand patients with rheumatoid complaints has been treated with intravenous streptococcic vaccine in the past nine years. These individuals have presented a wide variation in their clinical complaints and have consisted of a few children with chronic arthritis (Still's disease), adolescent individuals with variations of chronic arthritic symptoms and also those complaining of recurrent transitory muscle and joint pains over a period of time. Some of these had had clinical and atypical rheumatic fever and a few had cardiac damage. Most of the patients, however, were adults with varying rheumatoid manifestations. Most of these would fit what many choose to describe as rheumatoid arthritis although in our opinion hypertrophic changes are found so frequently as to make a dogmatic classification of symptomatic chronic arthritis inadvisable. There are also frequent fibrositic, neuritic and myositic conditions associated with clinical arthritic involvement. We did not treat asymptomatic individuals past fifty years of age, who nearly always show some hypertrophic, senescent, degenerative roentgenological and pathological changes in such locations as the spine and knees. We doubt the advisability of considering such asymptomatic conditions as arthritis. A number of older people were treated, however, and with apparent benefit who had significant symptomatic arthritis and who showed only hypertrophic changes on roentgenological examination. We did not treat individuals with arthritic symptoms apparently due to some specific agent such as the gonococcus, bacillus tu-

berculosis or of other probable known causes. It is difficult at times to make positive clinical identification of some of these conditions.

No one was treated unless symptoms had been present for two or three months or more because of the frequent spontaneous clinical cure of complaints of shorter duration. About 90 per cent had rheumatoid symptoms for more than a year prior to treatment.

A series of 1192 consecutive patients with symptomatic chronic arthritis was treated with intravenous streptococcic vaccine and analyzed as to clinical results following therapy (table 1). For purposes of study, we

TABLE I
Analysis of Clinical Improvement Following Intravenous Streptococcic
Vaccine Therapy for Chronic Arthritis (1192 Cases)

Months since beginning treatment	Under 6 months		6 months to 12 months		12 months to 18 months		18 months to 24 months		24 months and over		Entire series	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Definite improvement.....	171	81	131	69	226	77	173	75.5	194	73	895	75
Questionable improvement..	19	9	24	19	28	9.5	14	6.	33	12	118	10
No improvement.....	21	10	38	12	39	13.+	42	18.+	39	15	179	15
Totals.....	211		193		293		229		266			

advised no supportive therapeutic measures in this group. Many of these patients were followed for two years and longer. Improvement was based on such factors as decreased pain, decreased joint swelling, increased range of joint motion and the patient's ability to do more with his joints. The sedimentation rate was also of some value as an evidence of improvement. In this series 75 per cent seemed to be definitely improved, 10 per cent showed questionable improvement, and 15 per cent were unimproved. Improvement when present usually began within three to eight weeks after beginning treatment although in some instances improvement was noted only after a longer period of time and larger doses of vaccine. Quite frequently there has been rather sudden clinical improvement after three to six treatments with gradual improvement thereafter, and not infrequently interrupted by transitory periods of moderate exacerbation, which should not discourage continued treatment. Individuals with low grade clinical activity of long standing, seemed more slow in showing a favorable clinical response. In most individuals treatment was discontinued if no improvement was present after about four months' time. In individuals with low grade chronic spinal involvement a longer trial is usually given as these patients have often responded only after a longer period of time.

An important test of any therapeutic method in chronic rheumatoid disease is the observation of patients over a period of years. We have had the opportunity of observing a large number of such patients from two to five years after beginning vaccine. We have been impressed with the

infrequency with which individuals with an apparent early favorable response, have developed severe progressive arthritic involvement. These patients may have some recurrence in clinical activity when off of treatment for a time or even an occasional temporary flare up in activity while under treatment; but when under treatment either constantly or intermittently, they rarely go on to have severe progressive joint damage. On the other hand we have seen a significant number of those originally unimproved, go on to severe progressive involvement in spite of increased rest, physiotherapy and other general hygienic measures.

The high incidence of clinical improvement has seemed significant to us; however, reports have appeared with apparent similar improvement with procedures that have not been effective in our hands. Some of these such as colloidal sulfur and high vitamin D administration (200,000–300,000 international units per day), have been tried with patients who have not improved after vaccine therapy. A series of 35 such patients received colloidal sulfur in large doses over a period of two to three months without clinical improvement in any case. In a series of 16 patients receiving 200,000 to 300,000 international units of vitamin D for a period of three to four months only one reported significant improvement.

Such experiences and the criticism of a lack of controls made us feel that it was necessary to study vaccine effect in comparison with a control group of cases. Accordingly we have treated a series of 80 patients alternately without selection with vaccine and sterile normal saline solution. The only selection made in these cases was that they came from within a short radius of Minneapolis and that they would fit into a group that would be termed as rheumatoid arthritis by those using a definite classification.

Two unknown solutions were supplied us and labelled as A and B, one containing streptococcic vaccine (400 million per c.c.) and the other sterile saline solution. Alternate patients were treated with these two solutions by a number of different individuals and clinical progress notes made by them, at the time of each treatment. The patients were given eight weekly injections of increasing dosage as in the routine treatment and if improved continued to receive from 2 to 6 c.c. of material (800 to 2400 million, if of vaccine) at four week intervals. No patient in this series was followed less than four months, and some were followed more than two years. The majority were observed for more than a year. The criteria for improvement were less pain, less joint swelling, increased joint motion, an increased capacity for work and a decreased sedimentation rate. Patients were not considered as improved unless they had been better for at least several months and in most instances for a year or more. The records were analyzed independently by three members of the staff including Drs. George Leavitt and T. J. Bulinski, with concurrence in the clinical results from these records (table 2). There is shown to be a significant difference in the incidence of improvement in the two groups, 82.5 per cent of those receiving vaccine reporting definite improvement as compared with 40 per cent of the control

group receiving saline solution. It is impressive, however, that as many as 40 per cent receiving only saline solution seemed definitely clinically improved. There are probably several factors that account for this as: (1) the normal variations in the course of this disease, (2) the psychotherapeutic effect and, (3) that these patients were trying to get better, and that in spite of any definite advice were usually resting more and avoiding exposure and trauma. It is not unlikely that this third factor may have been the most important in explaining the clinical improvement in many in the control series. Considering the results of those receiving sterile saline solution, it can readily be understood why so many preparations, contrivances and manipulations have so often been seemingly responsible for miraculous improvement and cures in rheumatoid diseases.

TABLE II

Comparative Clinical Results in the Treatment of Patients with Chronic "Rheumatoid" Arthritis Receiving Intravenous Streptococcic Vaccine and Saline Solution

Clinical Result	A Series vaccine		B Series saline		$\frac{(P_1 - P_2)}{P_1 - P_2} *$	P^\dagger
	No.	%	No.	%		
Definite improvement.....	33	82.5	16	40	4.34	.00001
Questionable improvement.....	4	10	7	17.5	.98	.32809
No improvement.....	3	7.5	17	42.5	3.95	.00008
	40	100	40	100		

* $P_1 - P_2 / P_1 - P_2 = \frac{P_1 - P_2}{(P_1 Q_1)/N + (P_2 Q_2)/N} = \frac{(P_1 - P_2) N}{P_1 Q_1 + P_2 Q_2}$ which is the formula for testing the significance of difference between two percentages.

† The P is the probability of a difference between the two percentages as large or larger than the one observed being due to sampling errors. Thus .00001 means that there is 1 chance out of 100,000 that the difference between the two series is due to sampling errors.

REACTIONS

Reactions follow injections of intravenous streptococcic vaccine in some instances. A detailed study was made concerning the frequency and character of these reactions following one thousand injections of our usual strain of streptococcic vaccine. Table 3 shows that following one thousand injections, reactions were present in 202 cases; or that a reaction followed after about one injection in five. Reactions occurred most frequently that same day, usually coming on two to ten hours after vaccine was administered (175 reactions occurring the same day after 1000 injections). These were nearly always characterized by chills and a moderate fever, most frequently 99.6° to 101°. Reactions were present the following day 38 times after 1,000 injections of vaccine; and in only exceptional instances were reactions present later than 36 hours after treatment. The symptoms of reaction when present the following day were more variable than those occurring within two to ten hours. Some of the more common delayed symptoms were

TABLE III

Reactions from Intravenous Streptococcic Vaccine (Following 1000 Injections)

Incidence of reaction	
No clinical reaction	798
Clinical reaction	202
Total	1000
Time of reaction	
The same day	175
The following day	38
Total	213
Character of reaction	
Chills	145
Fever	112
Nausea	34
General aching	27
Fatigue and drowsiness	22

slight fever and chills, nausea, general aching, fatigue, drowsiness, and in a few instances diarrhea. Reactions seemed about as likely to occur after subsequent injections as after the first one. The majority of our patients were ambulant, and in only a few instances did reactions interfere with their usual activities. Patients experiencing reactions could usually minimize the symptoms by taking five or ten grains of acetylsalicylic acid two hours after treatment and repeating this at the onset of reaction symptoms.

It is of importance that the use of this strain of streptococcus vaccine carries little if any risk to the patient. We have had no definite fatalities from its use following over 100,000 injections in about 4,000 patients. We had one patient who died of amyloid disease, but considered it very unlikely that this was due to vaccine as the patient had a very severe extensive arthritic involvement; and we have had autopsies on several untreated arthritic patients who also had amyloid disease. We have used some strains of streptococcic vaccine (especially beta hemolytic strains) that have given some rather alarming reactions. The question arises as to the possibility of the use of vaccine aggravating an arthritic condition, meaning not an immediate transitory increase in joint pain which is of little significance, but an increase in the active clinical course of the disease. Theoretically an aggravation of the disease process on a basis of hypersensitivity should be not unlikely with a subcutaneous vaccine, and this has been reported by many using subcutaneous vaccines. This should be theoretically unlikely with intravenous vaccine. In our experience the number of individuals who have shown a rapid clinical progression of their disease following intravenous vaccine have been so few as to make it seem probable that they have simply been unaided by vaccine and that the disease has run its course. It is of course possible that in a few instances this may not be the explanation.

We have found no correlation between the degree of clinical improvement and the reactions experienced. Reactions have chiefly been used as a guide in determining the advisability of giving larger doses of vaccine than

in the usual schedule. A moderate reaction does not interfere with our anticipated plan of increased dosage, and on the other hand we often increase the dose more rapidly when no reactions are present.

We advise not treating pregnant women with arthritis because of the remote possibility that such treatment might contribute to an abortion and also to avoid criticism of those who might abort otherwise and consider vaccine as being responsible. We have treated very few individuals with clinical evidences of coronary sclerosis although there is probably very little chance of a reaction precipitating an anginal attack or coronary thrombosis. Following vaccine, individuals with glomerulonephritis have at times shown increased red cells in the urine and in one instance the treatment seemed to precipitate a gross hematuria, so that we do not use intravenous streptococcic vaccine in arthritic patients with nephritis.

COMMENT

Our experience with intravenous streptococcic vaccine following the method outlined, has convinced us of its therapeutic value for many patients with rheumatoid conditions. This is based on the treatment of over 4,000 patients in the past nine years, and our experience with a control series receiving intravenous saline solution injections. It is difficult to evaluate the use of vaccine or any type of therapy in an individual case of rheumatoid disease because of the variable clinical course. It is especially inadvisable to draw conclusions from patients with relatively acute symptoms and those with a recurrent transitory condition or with symptoms of but a few weeks' to a few months' duration.

In the treatment of any patient with chronic rheumatoid complaints, careful consideration should be given to the individual problems presented such as contributing etiological factors, the severity of the condition, and the patient's social and economic circumstances. If no known specific etiological agent is responsible for the condition, it has been our practice to give the patient a trial of intravenous streptococcic vaccine. This treatment is by no means a cure-all, nor is it effective for all patients but has seemed more efficacious than any other single method that we have used. There are a number of other general therapeutic procedures to be considered in the treatment of rheumatoid disease such as: (1) individual regulation of rest and activities, (2) the avoidance of cold, exposure, and trauma, (3) palliative and supportive drug therapy, (4) possible curative medications (gold salts, sulfur, chaulmoogra oil, bee venom, high dosage vitamin D, etc.), (5) physiotherapeutic procedures, (6) individual dietary regulation, (7) the consideration of alleged foci of infection, (8) roentgen-ray therapy, (9) foreign protein therapy, (10) climatic change, and (11) the prevention and correction of deformities.

Our experience has led us to believe that the removal of alleged foci of infection such as teeth and tonsils has been much overemphasized, especially

for individuals with well established arthritic disease. If streptococci are etiological agents as many believe, it seems impossible to eradicate exposure to organisms that are constantly present in the mouth, nose, throat and bowel. In some instances we have seen marked aggravation of an arthritic process following the removal of teeth and tonsils and have considered it advisable to give a course of vaccine prior to such procedure in patients with rheumatoid disease.

Patients with chronic rheumatoid disease, who have not improved after prolonged observation and treatment with intravenous streptococcic vaccine, offer a critical trial to other therapeutic agents. We have treated a significant series of such patients with colloidal sulfur, chaulmoogra oil, high vitamin D therapy (200,000 to 300,000 units per day), bee venom derivatives, and gold salts. None of these have seemed to be followed by definite clinical improvement with the exception of gold salts. The gold preparation used by us was sodium aurothiomalate (myochrysine), in most instances giving 25 milligram doses intramuscularly at weekly intervals for a series of 15 to 20 injections. Definite clinical improvement of some degree has been observed in about 75 per cent of these patients.

Gold therapy as used at present is by no means a safe procedure for routine use. We have observed exfoliative dermatitis in five of the first 35 patients treated, and there are other serious toxic or allergic reactions at times. Our criteria for the use of gold therapy are as follows:

1. The patient has severe rheumatoid disease.
2. An adequate trial of intravenous streptococcic vaccine has been used without clinical benefit or with inadequate improvement.
3. The patient is fully advised of the dangers and assumes the risk of treatment.

There have been a number of different gold products tried in an effort to reduce the toxic effects. Sabin and Warren have recently reported on the trial of calcium aurothiomalate and report it as much less toxic than the sodium salt in mice. A trial in man is necessary before drawing any definite conclusion, however, in view of the probable allergic factor.

SUMMARY

1. More than 4000 patients with chronic rheumatoid conditions have been treated by us with intravenous streptococcic vaccine in the past nine years without a definite fatality from treatment.

2. A series of 1194 were treated by this method alone and the results analyzed as to clinical improvement. Seventy-five per cent seemed definitely improved, 10 per cent questionably improved and 15 per cent unimproved following treatment.

3. A series of 80 patients who could be described as having "rheumatoid arthritis" was treated alternately with unknown solutions of vaccine and

sterile saline solution. In the group receiving vaccine, 82.5 per cent seemed clinically improved as compared with 40 per cent of those receiving saline solution. A statistical study indicates this as being a significant difference.

4. The high percentage (40 per cent) reporting significant improvement after sterile saline solution injections affords some explanation of the striking clinical improvement reported by some patients with rheumatoid conditions, after all manner of procedures.

5. It is our opinion that intravenous streptococcic vaccine, as used, is of value in the treatment of many individuals with chronic rheumatoid disease; but that it is by no means a cure-all, that it is ineffective in some cases, and should be combined with such general procedures as seen indicated in each individual case.

BIBLIOGRAPHY

1. *a.* CLAWSON, B. J., and WETHERBY, MACNIDER: An experimental basis for intravenous vaccine therapy in chronic arthritis with a summary of results obtained in patients, *ANN. INT. MED.*, 1932, v, 1147.
b. WETHERBY, MACNIDER, and CLAWSON, B. J.: Intravenous streptococcic vaccine therapy in chronic arthritis, *Jr. Am. Med. Assoc.*, 1932, xcvi, 974.
2. REIMANN, H. A., and EKLUND, C.: Long-continued vaccine therapy as a cause of amyloidosis, *Am. Jr. Med. Sci.*, 1935, cxc, 88.
3. SABIN, A. S., and WARREN, J.: Therapeutic effectiveness of a practically non-toxic new compound, *Science*, 1940, xcii, 535.

METABOLIC CRANIOPATHY: HYPEROSTOSIS FRONTALIS INTERNA *

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THE entity generally referred to as *hyperostosis frontalis interna*, the Morgagni syndrome, or the Stewart-Morel syndrome, and recently renamed metabolic craniopathy by Moore⁴³ is not new to medical literature. It has been the topic of occasional discussion and considerable confusion in European writings since its description by Morgagni.⁴⁷ Though the entity has not always been clearly defined, its notation may be recognized in the reports of numerous authors through the last century and a half, during which time it has been included in a number of craniopathies, and in several other named syndromes. Thus, it has been described as a form of cranial exostosis, of enostosis, of osteophyte, and of senile hyperostosis. Although each such group appears to have a reasonable relationship to this bony change, all, at least until clarification of the concept in the literature of the past 10 years, fail to emphasize, as is done by Moore's term, the truly constitutional nature of a disease in which the bony changes can be considered only a pathognomonic part and a sine qua non to its diagnosis. The Morgagni syndrome, including, with the bony changes, obesity, and virilism, and the Stewart-Morel syndrome which added insanity, likewise failed to emphasize the entire complex, yet integrated the systemic and particularly the endocrine aspects of the disease. The new term should be of assistance in directing further thought upon the subject. Such emphasis upon a clinical entity is justified by its not uncommon occurrence and, therefore, its importance. On the other hand, it is probable that the entire concept of the disease may later become submerged into its proper niche of constitutional and developmental diseases on an endocrine basis, as is suggested by the work of Mortimer and his associates.^{48, 49} In the meantime, however, attention to this entity is not objectionable, provided that a proper view of its true relationship is not lost.

HISTORICAL

Interest in the disease has been continuous since its first known description by Morgagni and Santorini in 1765.⁴⁷ The case reported at that time was typical of the syndrome as known today. Discovery of this pathologic change in even earlier skulls has since been reported, however, by Henschen.²⁸ Thus, museum skulls from early Nordic graves, as well as the skull of the woman in the Osebery ship, have shown typical changes. Autopsy findings of *hyperostosis frontalis interna* in the case of a priest executed for quadruple murder in 1785 were described by Moreau.⁴⁴ Lobstein included this

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entity among intracranial osteophytes in 1833,³⁷ and Rokitanski,⁶¹ in 1850, undoubtedly included it among his "puerperal osteophytes" which he popularized in the literature of the latter half of the 19th century, but which obviously related mainly to changes other than *hyperostosis frontalis interna* as understood today. These changes had been mentioned in 1844 by Hauff, who is quoted by Schiff and Trelles.⁶⁵ It is probable that, along with true metabolic craniopathy and membranous dural calcification, Rokitanski included with his puerperal osteophytes instances of osteitis deformans, acromegaly, tuberculosis, inflammatory osteitis, and circumscribed enostoses. Puerperal osteophytes received occasional mention by Wilkes in 1857,⁶⁰ by De Lee in 1913,¹² and by Williams in 1923,⁸¹ all authors including entities which today may be differentiated from "metabolic craniopathy," by reason of its more fully understood nature.

Although in later writings descriptions of the bony changes of metabolic craniopathy have been limited to the skull, Rokitanski described also an ankylosis of the vertebrae as by a "flow of material" over their anterior surfaces.⁶² It is possible that this may have referred to an accompanying ligamentous calcification as found in the Marie-Strumpel type of spinal arthritis. Birkett,⁴ in 1869, noted *hyperostosis frontalis interna* in a discussion of Rokitanski's osteophytes in a Guy's Hospital Report, and Sauvage, in 1870, discussed its pathogenesis.⁶³ Legouest and Servier,³² in 1879, quoted Virchow on the subject, and presented museum specimens. Bevan Lewis, in 1889,³ classified 54 presented cases according to location of the changes in frontal, parietal, or occipital regions. Thereafter, numerous anatomical and pathological studies were presented, including especially those of Beadles,² Clauston,¹⁰ Susse,⁷⁶ Zander,⁸² Fuchs,²¹ Humphrey,²⁹ Reichardt,⁵⁷ and Dietz.¹³ These studies formed the basis for differential diagnosis on pathological grounds, a trend which has continued to date,^{19, 22, 23, 26, 30, 40, 56, 57, 61, 66, 74, 76, 77, 78} clarifying the confusion which rendered of little statistical value the literature before 1900, especially that relating to the puerperal osteophytes.^{11, 22}

Clinical recognition was tardy, dependent as it necessarily was upon the development of roentgen-ray detection of the pathognomonic internal cranial changes. Stewart,⁷³ in 1913, performed an autopsy on a patient described two years earlier in his notes as showing unusual clinical features which we now recognize as those of metabolic craniopathy, but the case was not reported until later. Naito in 1924,⁵⁰ Schuller in 1924,⁵¹ Casati in 1926,⁷ and Leri and Cottenot in 1926³⁴ made initial reports on the radiographic features of metabolic craniopathy. Since then clinical recognition has been more general mainly because of studies of English and French neuropsychiatrists, an interesting commentary on the symptoms presented by the patient. It was in 1930, however, that Morel described the first living case of the disease⁴⁵; and his report was followed closely by others from VanBogaert in 1930,⁷⁹ and Schiff and Trelles in 1931.⁶⁵ The European literature has since

contained frequent reports featuring the critical writings of Stewart,⁷³ Greig,²⁴ Dressler,¹⁵ and Henschen.^{25, 26, 27} The American reports, which have included careful radiographic descriptions, began to appear in 1935 with Moore's studies.^{41, 42, 43}

Particularly important in the clarification of the concept of metabolic craniopathy have been the writings of Stewart,⁷³ Carr,⁶ and Henschen²⁵ who have critically reviewed all past cases and have added new observations in numbers sufficient to permit appreciation of the importance of the disease and an adequate cataloging of its clinical features. These features are now sufficiently delineated and characteristic to suggest that the radiographic findings may no longer be essential to the diagnosis of the malady, and at times may even be among the less significant features. It now appears probable that instances of the disease which lack the notable cranial changes are going unrecognized for want of an appreciation of its other criteria.

Because of indistinct concepts of the disease prior to 1900 and because of confused cross-references and tabulations in many of the published reports, it is difficult to estimate the total number of authentic cases to date. Henschen²⁵ notes bibliographic reference to 225 female and eight male autopsies, and added 66 museum specimens of his own. He also added 28 personally observed cases to the three living ones reported up to that time in the literature, excluding the 72 cases reported by Moore after retrospective examination of roentgen-rays. Other reports have concerned single cases or smaller series. The case longest observed and reported in the literature was the two year observation of Stewart noted above, during which time change in bony appearance was noted; the next longest was that of Eisen,¹⁷ whose study covered 15 months.

In all, perhaps something over 300 autopsy and museum specimens have been reported since 1900, and approximately 175 clinical cases have been described, making reasonable allowance for duplication in cross references. As indicated before, it is impossible to estimate the number of true cases of metabolic craniopathy in the confused literature appearing before 1900.

Practically the entire literature on the subject has been directed to inductive analysis of the protean clinical and pathological features of the entity, and has ultimately arrived, past several interesting digressions, at a rather satisfactory conclusion that endocrine, especially pituitary, dysfunction and the associated dysmetabolism are responsible for the disease. The more interesting, therefore, is the careful descriptive work of Mortimer, Levene, and Rowe⁴⁹ who have analyzed deductively a large series of pituitary cranial dysplasias. In their description and classification are to be found undoubted reference to *hyperostosis frontalis interna*, though it is never referred to as such. It would thus appear that an important meeting of effort had occurred, and further investigation will undoubtedly broaden the knowledge of the concept as a whole and determine its proper place and relative importance among endocrine and metabolic diseases.

THE SYNDROME

It is apparent from the literature that the clinical features of the disease are multiple, and that no one feature is indispensable to the syndrome. It is even probable, as already stated, that the bony changes themselves may be absent from some cases. Roentgen-ray findings, however, remain the most characteristic and constant feature recognized to date, and, when found, are

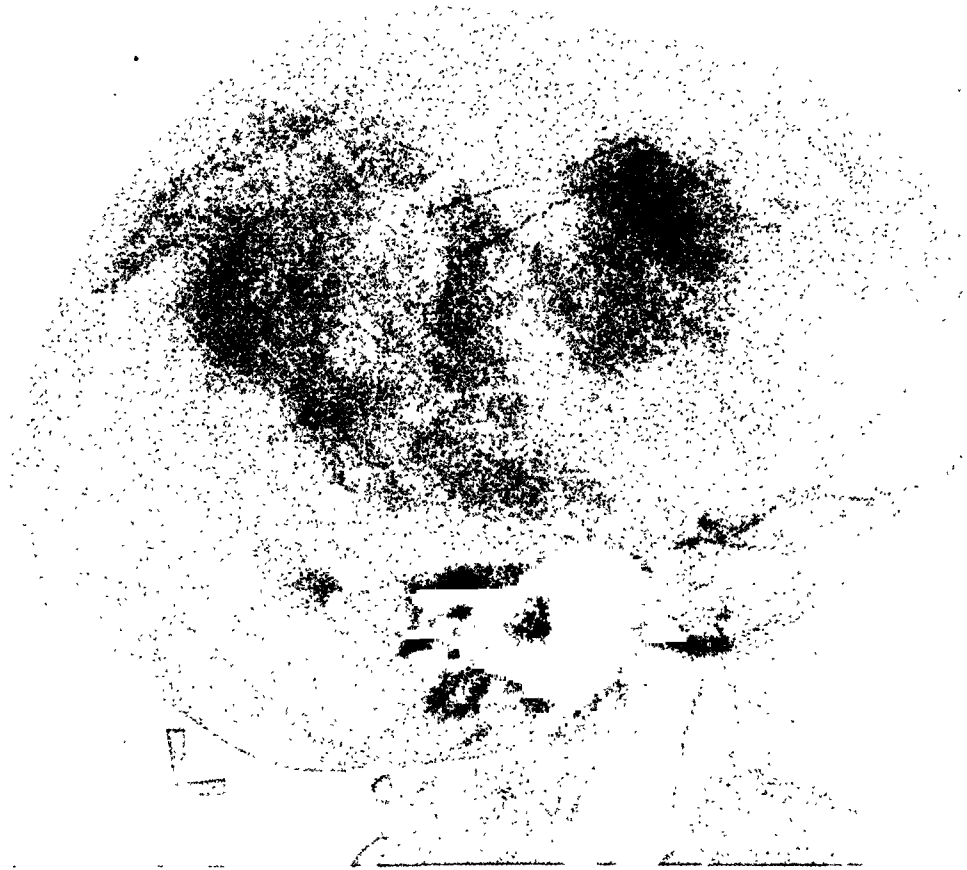


FIG. 1. Lateral roentgenogram of skull of case 12, showing frontal hyperostosis interna, generalized thickening of the calvarium, and calcification of falx. A murderess with marked character changes.

considered pathognomonic by Casati^{7,8} and others. Bevan Lewis first classified the bony changes topographically as frontal, parietal, and occipital, a grouping more fully expanded and defined by Moore as follows:

1. *Hyperostosis frontalis interna*, a non-inflammatory deposit of new bone on the internal table of the *squama frontalis* and extending occasionally to the orbital plates, the falx, the *squama parietalis* (figures 1, 2, and 3). The base of the skull, the longitudinal sinus, and all suture lines are usually

spared,⁴⁰ but involvement of the middle fossa by associated osteoma has been described by Morel and in one of our own case reports (case 27). The internal surface of the skull may vary in appearance from that of small overlapping waves to "mountains in relief," with increase of the bony thickness to 2 cm. at times.⁶⁰ A thickening of the diploë occasionally occurs, but the external table is spared. The hyperostoses are almost invariably symmetrical, although exceptions, one of which is described in the present paper (case 24), have been reported.⁵⁸ The rapidity of growth is usually imperceptible, suggesting that active changes may have preceded the onset of symptoms. Progression in roentgen-ray appearance of the lesions has, however, been described by Schiff and Trelles,⁶⁵ Eisen,¹⁷ Reider,⁵⁸ and de Lehoczy,⁸³ and occurred in two of our own cases (cases 1 and 14). Notable reversibility of bony changes has not been noted, however, even where clinical improvement has been marked. Such changes were shown by Moore⁴¹ to have an incidence of 1.44 per cent among skull roentgen-rays, and are included by Mortimer in the fourth class of pituitary calvarial dysplasias.⁴⁰

2. *Nebula frontalis*, consisting in increased density and thickness of the diploë of the *squama frontalis* only (figure 4). This form was found in 1.14 per cent of Moore's roentgen-rays. Progression has been noted in such cases after periods of several months.

3. *Hyperostosis calvariae diffusa*, a thickening of the diploë of the entire vault (figure 6) without involvement of either table, and with a roentgen-ray incidence of 0.6 per cent. The normal vascular channels of the calvarium are markedly deepened. Such changes are found in Mortimer's type II (pituitary cranial dysplasias), along with those of group 2 just described, and group 4 of the present classification.

4. *Hyperostosis frontoparietalis*, probably an intermediate stage between groups 2 and 3, with a roentgen-ray incidence of 0.3 per cent.

5. A thinning of areas of the frontal bone or other cranial bones in association with one of the first four groups, noted pathologically by Greig,²⁴ and Dressler,¹⁵ radiographically by Naito,⁵⁰ and more recently reported by Moore,⁴³ and seen by us (case 14). These instances are also reasonably explained by Mortimer.

This classification, the first American contribution to the subject, is based on a tremendous roentgen-ray experience, and will assist in clear thinking. Distinction between sub-groups, however, particularly between numbers 2, 3, and 4, appears somewhat arbitrary, and care must be exercised lest thought be confused rather than simplified. It is readily understandable, of course, that only group 1 would have met frequent description in the literature before the widespread use of roentgen-ray. We have seldom found the last four groups unassociated with group 1, however, and feel that they probably represent variations of a central theme.

It is thus apparent that the outer table is usually undisturbed in all forms of the disease and that the external skull volume remains unchanged. A

slight flattening of the external frontal convexity was noted as a progressive change in one of our own cases after 10 months of observation (case 1). The symptom complex appears to be independent of the roentgen-ray type of lesion present.

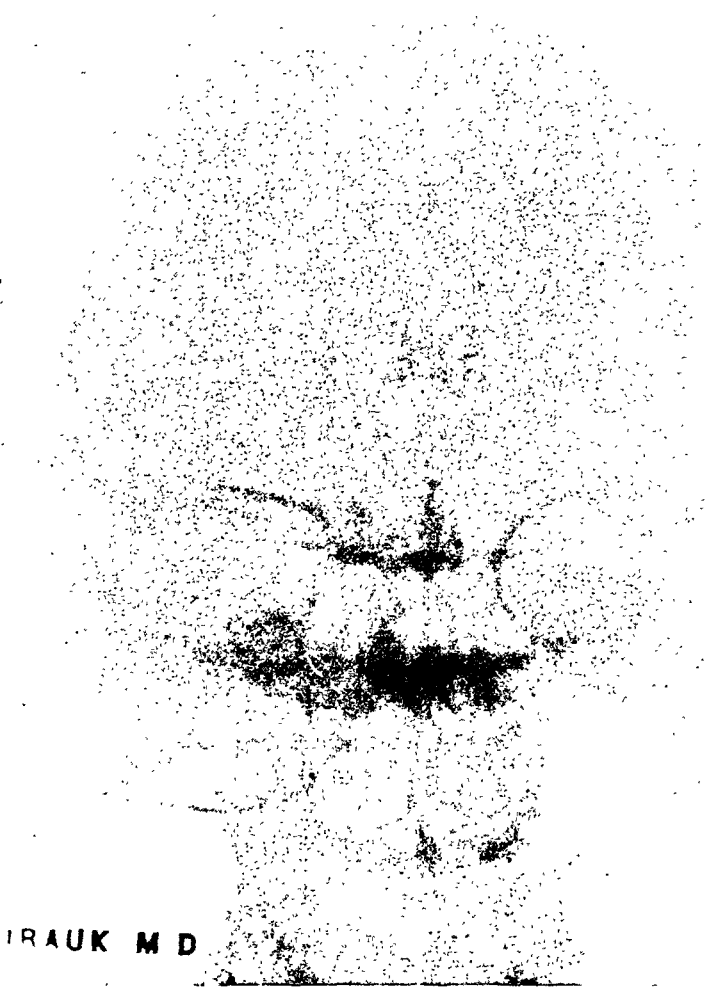


FIG. 2. Anteroposterior roentgenogram of same skull as figure 1 (case 12).

Extracranial bony changes were described by Rokitsanski in the form of a fusion of the anterior surfaces of the vertebrae,⁶¹ and by Carr as a diffuse osteosclerosis of the entire skeleton.⁶ Rogers has also noted slight extracranial bony changes.⁶⁰ Moore, however,⁴² finds extracranial alterations of the skeleton merely those to be expected among the skeletal changes of the age groups involved in this disease, or as features of associated acromegaly or other incidental states.

Obesity of a simple or pituitary type has been found in 50 per cent or more of the patients with metabolic craniopathy^{41, 65} but may be minor in degree or completely absent. The breasts have been reported to be typically large and pendulous,⁴¹ but not always so. Virilism and hirsutism, often marked, may also be minor or absent. The association of bony changes, obesity and virilism constitutes the Morgagni syndrome under which name much literature on the subject has appeared.

Mental changes have been generally noted in the symptomatology of the disease, and, when associated with obesity and the bony changes, constituted the Stewart-Morel syndrome. Complete mental incompetence, though described,²⁵ is uncommon, the involutional symptoms of insomnia, depression, and nocturnal agitation⁶⁸ being more frequent. Memory defect was found by Carr⁶ in 88 per cent of the cases, and amnesia, hallucinations, disorientation, and ideas of grandeur have all been noted.^{65, 40} Insanity, when it does occur, is of ill-defined type, and may be intermittent.¹⁰ The patient of Schiff and Trelles was noted to have a "revenge psychosis."

Neurological changes are commonly found with metabolic craniopathy. Convulsions have been noted in 35 per cent of cases.⁶ Loss of smell, fifth nerve neuralgia, seventh nerve weakness and paralysis, motor speech difficulty, weakness of an extremity, and transitory hemiparesis and hemiplegia have all been described.^{15, 25} Trigeminal herpes was noted by de Lehoczy; and unilateral facial neuralgia complicated one of our own cases (case 8). Ataxia in station, and gait of a type with wide base and marked propulsion have been noted by Schneider⁶⁸ and others, and have appeared prominent in our series. Exaggerated reflexes have been noted.⁶ Muscular asthenia has been found in 48 per cent of cases and other muscular defects in 17 per cent.⁶ Vertigo is reported in 64 per cent, and visual disturbances, including nystagmus and hemianopsia, in 41 per cent. Confusion, irritability, and senile dementia have been listed, and juvenile epilepsy was reported by Shattock.⁶⁹

The malady is stated by Moore⁴¹ to be found in the female in 98 per cent of cases, but the literature and our own series contain several male patients. In many of these, however, cranial injury appears to have been sustained.

The usual age of diagnosis has been in the fifth decade, but Stewart⁷³ has reported the disease in a 19 year old male, and Leri and Lievre reported association with Little's disease in a child of five years.³⁵ Our own youngest patient was a 13 year old male (case 7). Cases have been reported with onset of symptoms as late as 95 years.²⁵

Metabolic aspects of the disease are emphasized by the repeated observations of polyphagia, polydipsia, polyuria, and elevation of glucose tolerance. Hypercalcemia and alterations in blood pH were reported by Schneider.⁶⁸ Myotatic irritability and generalized convulsions suggest that some of these patients may be included in that spasmophylic group resulting from low utilization of calcium, as suggested by Timme in the discussion of

Carr's paper.⁶ Moore, however, found normal calcium and phosphorus values in the blood.⁴²

Headache has characterized 82 per cent of the cases of some series.⁶ This may be either intermittent or constant, and is usually frontal and bilateral, though occipital and parietal localization appears in many case reports, and

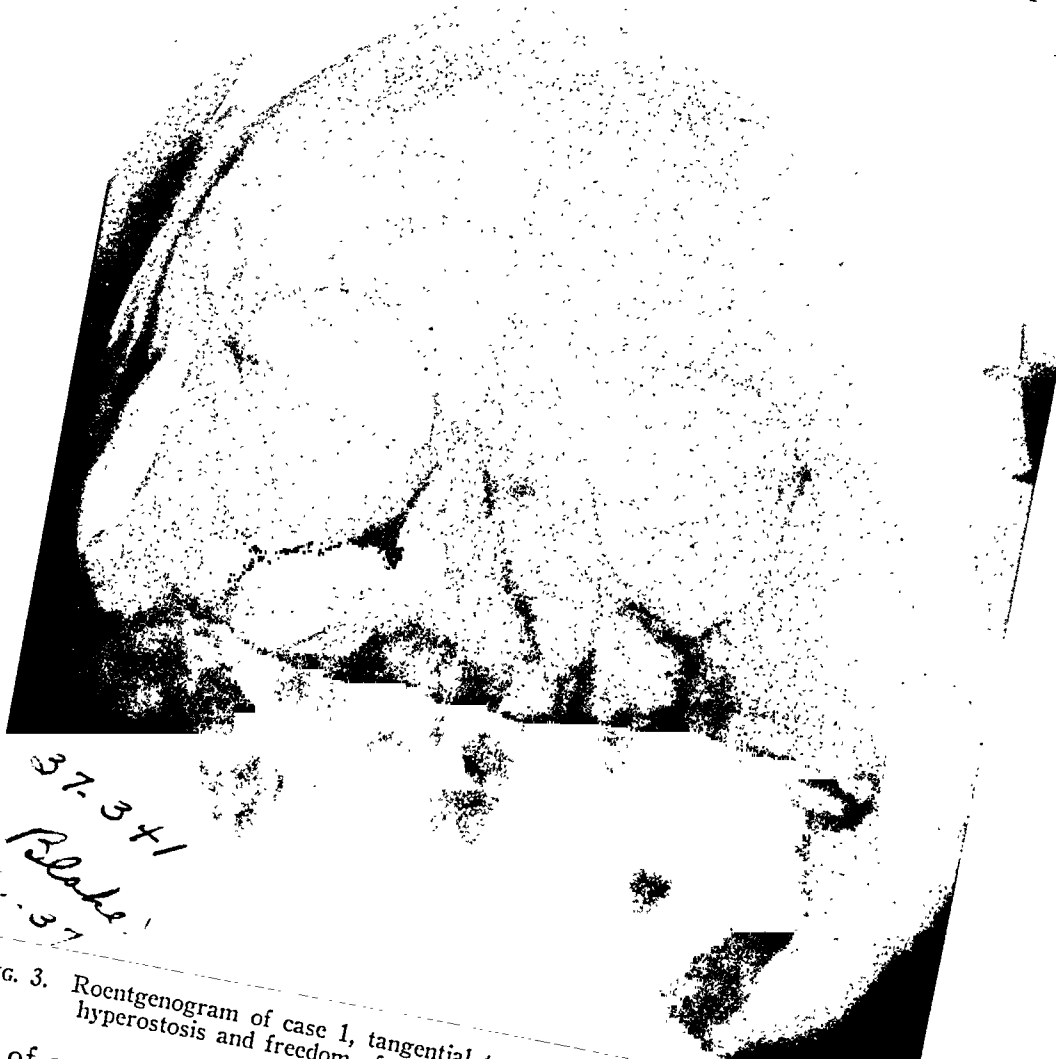


FIG. 3. Roentgenogram of case 1, tangential to frontal bone showing symmetry of hyperostosis and freedom of longitudinal sinus from involvement.

in one of our own patients it was unilateral. Interestingly enough in many case reports headache has existed continuously after a given trauma, though the bony changes absent at roentgen-rays immediately post-traumatic were shown to have appeared in other films months or years later. This suggests that the headaches may not be the result of the bony changes, but that both may follow a basic, possibly pituitary, injury.

Hypertension has been stressed by some authors, but its occurrence in only 11 per cent of cases according to Carr⁶ is probably not much above the normal expectancy for the age groups concerned.

Associated endocrine changes are common in the literature of the subject. Menstrual disturbances have been noted in 76 per cent of female cases; 50 per cent had had one or more pregnancies.⁴² Thyroid abnormality, particularly insufficiency, has been described in 4.4 per cent of cases; hyperthyroidism was noted by Casati.⁸ Pituitary influences are seen in the metabolic and nutritional features already referred to. Thus, diabetes insipidus has complicated metabolic craniopathy,⁶⁸ as well as adiposogenital dystrophy. Acromegaloid characteristics and true acromegaly have been noted, with attendant generalized bony changes.^{25, 2} Naito included an acromegalic patient with pituitary tumor, and the same condition has been noted also by Greig,²⁴ Beadles,² and Henschen,²⁵ eosinophilic, basophilic, or chief cells predominating variously. Moore noted a solid hypothalamic tumor,⁴¹ and Stewart⁷³ described a sclerotic pituitary enlargement with chromophile deficiency, and in another instance an atrophy of all normal pituitary components with replacement fibrosis. Most pituitary involvement has apparently been associated with insufficiency of that gland, at times after a preliminary period of hyperfunction as attested by acromegaloid changes.

Morel noted a mild chronic leptomeningitis with granular atrophy of the ependyma of the third ventricle.⁴⁵ Alzheimer's disease, with typical post-mortem findings, has been noted in association with metabolic craniopathy by Schneider,⁶⁸ and by Reider,⁵⁸ but no opinion as to causative relationship has been hazarded; the latter's case was interesting because of the rapidity and the unilateral localization of the bony changes. Associated Pick's disease has been noted by Morel.⁴⁰ Little's disease in a child was found by Leri et al.³⁵ associated with cephalic arrest attributed to premature birth at six and a half months; again an etiological relationship was not inferred.

Schiff and Trelles,⁶⁵ James³¹ and others noted the apparent relationship of hyperostosis to head injury. In a great proportion of the male cases in the literature this relationship seems too intimate to be dismissed lightly. The sequence suggested an "hysterio-trauma" to Schiff and Trelles in their case. They suggest, however, that the original lesion may be an infundibuloglandular injury, with resulting dysmetabolism, ending in hyperostosis.

One case with complicating achondroplasia has been reported.²⁴ Syphilis and race have been shown to be of no significance etiologically.⁴¹ Morel's first case had agenesis of a kidney.

It is apparent from the above that, as suggested by Morel, and by Perkins,⁵⁸ the clinical features of metabolic craniopathy may be divided into groups comprising: (1) those changes unmistakably endocrine and metabolic in nature, suggesting an infundibulo-pituitary origin; (2) those changes attributable to local pressure of the hyperostoses, including brain changes; (3) those symptoms found as a result of the normal degenerative changes in

the age groups concerned. Still other features described in association with this disease probably have no more than a coincidental relationship. The apparent dissociation of reported manifestations of the disease is better understood if such a grouping is kept in mind.

ETIOLOGY

It was perhaps natural that *hyperostosis frontalis interna* should first be regarded as an unusual feature of an already known disease. Marchand,³⁹ although recognizing that not all cases could be so considered, thought that some were due to syphilis. Bonnamour and Jamin⁵ and Picard⁵⁴ suggested

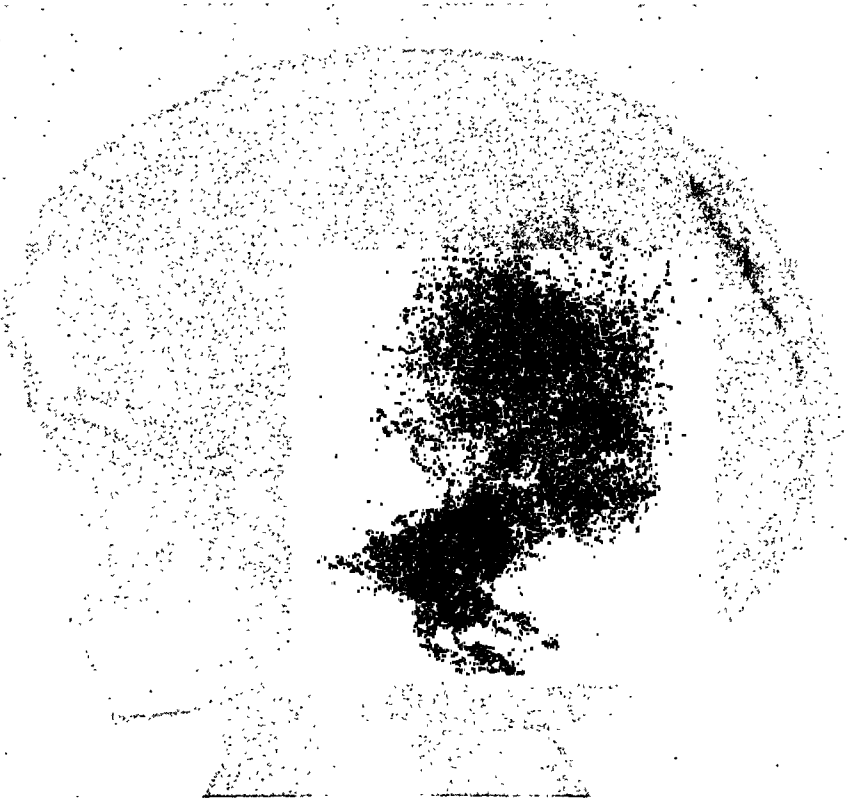


FIG. 4. Lateral roentgenogram of case 1 at first observation. No change in external contour of frontal bone. Type II of Moore's classification.

that metabolic craniopathy was an aberrant form of Paget's disease; Henschen, however, could find no microscopic resemblance.²⁵ It has already been pointed out that Rokitanski and other early observers did not clearly differentiate between this disease and several others.

Some authors have invoked an inflammatory background in explanation of the entity. Thus, Beadles in 1896,² Clauston in 1898,¹⁰ and Shattock in 1913⁶⁹ considered that the excessive bone formation might be due to dural congestion in the specific areas. This view has been shared more recently by

Knaggs.⁷¹ Infection as a cause of such congestion has not been prominently mentioned except as the disease has occasionally been considered an unusual form of syphilis, tuberculosis, or other known infectious entity. The Italian school, however, including Bartolotti, Nicotra, Novali and Rizzo, quoted by Pende,⁵² considered the hyperostosis to be due to an osteoblastic response of the bone forming cells, or an ossifying pachymeningitis due to contiguous and lymphatic stimulation, resulting from chronic frontal sinusitis. This contention would appear to be invalidated by the failure to demonstrate frontal sinusitis to any marked degree in any of the large series of cases so far reported.

More generally a mechanical cause of congestion has been proposed. This has included external trauma which, as has been pointed out before, appears in many case histories to be associated prominently with the onset of symptoms. More careful inspection, however, reveals the inadequacy of this explanation because of the large number of cases without a history of injury. In the opinion of most writers the effect, if any, of trauma in the production of metabolic craniopathy has been through intermediate endocrine disturbances following injury to the pituitary gland or adjacent structures, with resulting disorders in calcium and fat metabolism leading to hyperostoses and these in turn to the psychic and encephalitic features of the disease.^{35, 66} This concept of the indirect endocrine effect of external injury may be importantly confirmatory of the spontaneous endocrine origin of other cases of the disease.

Schmidt,⁶⁷ conceding the inadequacy of external injury as a total explanation of hyperostosis, suggested that the repeated tugging on the dura by the arachnoid vessels in time with the pulse might lead to significant inflammation. The basis for such tugging was not explained, and the suggestion is at present considered of possible importance only in determining the location of bony changes.

Morel, although recognizing that the disease is essentially the result of generalized calcium dysmetabolism, suggested that its frontal location might be conditioned by the constant tension of an adherent dura. Similarly, the backward drag of the brain on its meninges in the dorsal recumbent position assumed by many aged persons long confined to bed has been suggested as a factor.³⁸ The uniform symmetry of the diseases would, however, be unexpected in view of the large proportion of senile persons assuming a lateral fetal position by choice. Furthermore such factors cannot pertain to the younger and more vigorous persons more recently reported in the literature and among our own cases.

Naito and Schuller⁵¹ and Dressler¹⁵ suggested that the bony changes of metabolic craniopathy might be compensatory to arteriosclerotic or senescent brain atrophy. Dressler found such changes also in young persons with cachectic brain atrophy and in cases of progressive paralysis. Authors from Sauvage in 1870⁶³ to Erdheim in 1935 have described brain atrophy and

diminished internal skull volume in both male and female aged persons, with thickening of frontal and parietal bones and at times of the entire skull, but different in many respects from metabolic craniopathy and lacking its associated features, though presumably dependent upon senescent pituitary atrophy. Henschen, furthermore, was unable to demonstrate important differences in brain weights among 131 autopsy cases with and without hyperostoses, and the theory today is largely of historical interest. A suggestive relationship of hyperostosis to frontal lobe atrophy is suggested by one of our own patients (case 24).

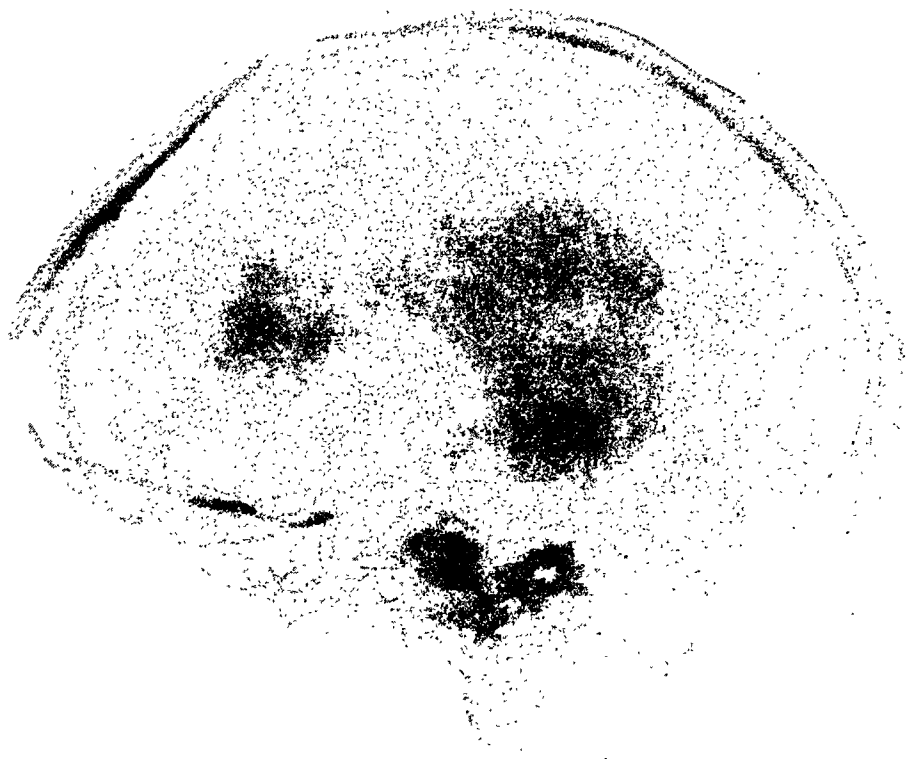


FIG. 5. Lateral roentgenogram of case 1 fifteen months after figure 4, showing increase in frontal hyperostosis, incipient parietal hyperostosis, and flattening of external contour of frontal bone.

The relationship of metabolic craniopathy to the puerperal osteophytes has been of great importance in the formation of theories of pathogenesis. Schmidt⁶⁷ and Rokitanski⁶¹ considered that such osteophytes, from which they did not differentiate hyperostoses, were formed in the dura and later became "soldered onto" the skull. Rokitanski found such changes associated with pregnancy as early as the third month. He felt that they were added to by subsequent pregnancies, particularly at the site of vascular bony tissues. Three stages could be recognized: a white or red gelatinous exu-

date, vascular, and easily removed in the fresh skull; later, a soft flexible cartilaginous layer; and finally, smooth, porous, calcific lamina, firmly adherent to the inner table of the skull. Although his remarks concerned the puerperal osteophytes, some of his illustrations were undoubtedly those of metabolic craniopathy. Greig²⁴ considered that "the formation of such osteophytes is unlikely to occur in pregnant women who have a physiological outlet for their calcium; but after the birth of a child, especially if the mother is not nursing the child, and so losing calcium in her milk for the benefit of the infant, an excess of calcium might favor the deposition on avascular

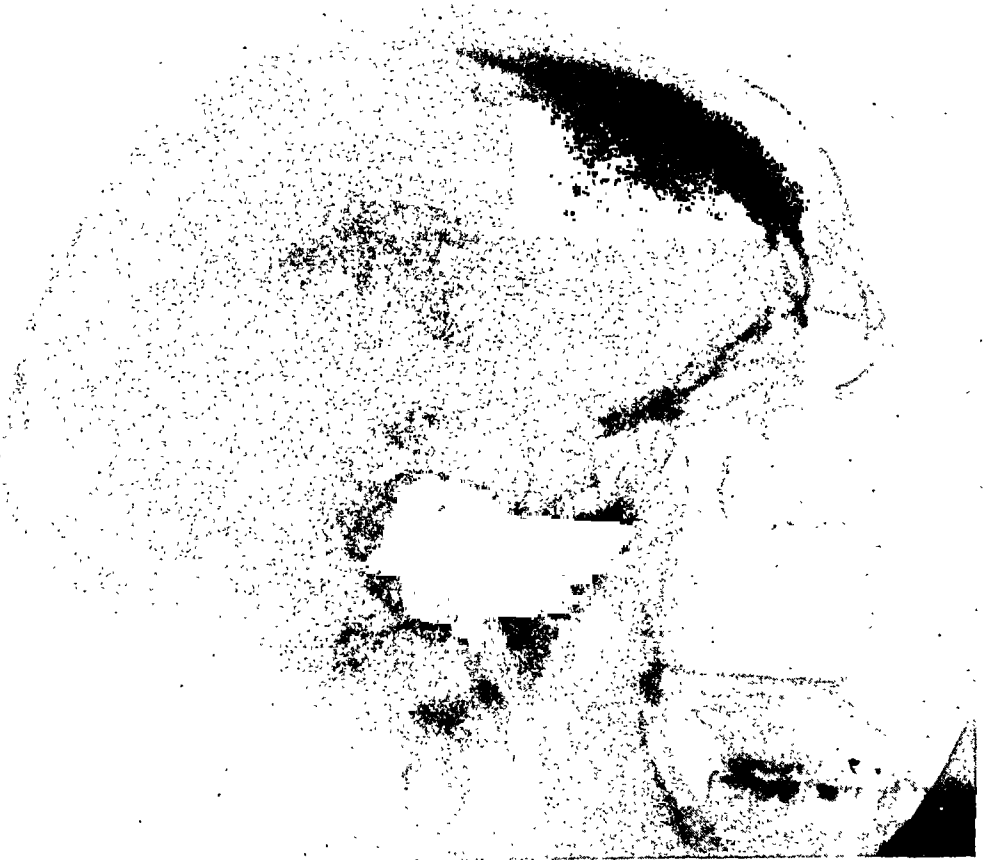


FIG. 6. Lateral roentgenogram of skull of case 9. Thickening of entire vault, especially marked in frontal areas. Type III of Moore.

structures, and even the formation of bone in specific avascularized areas." Such deposition might also follow saturation of the blood with calcium resorbed in chronic invalidism or fracture, especially when excretory powers are failing, as occasionally happens in senility. The diploë of the frontal bone, however, would hardly be an avascular structure in which calcium deposition might thus be expected, and the long life of many patients after the discovery of well developed hyperostosis would contradict a failure of

excretory powers. Thus, both bony vascularity and avascularity have been considered important by different authors in the etiology of the disease. Greig thought such depositions to be about the diploic vessels rather than the meningeal circulation, inasmuch as osteophytes, from which he did not clearly distinguish the hyperostoses, are not found in the absence of diploë, a fact noted also by Chiari.⁹

Furthermore, although the puerperal osteophyte was stated by Dreyfuss,¹⁶ who is quoted by Williams,⁸¹ to occur as frequently as in every third pregnancy, and was subsequently thought to follow dyspituitarism, such observa-

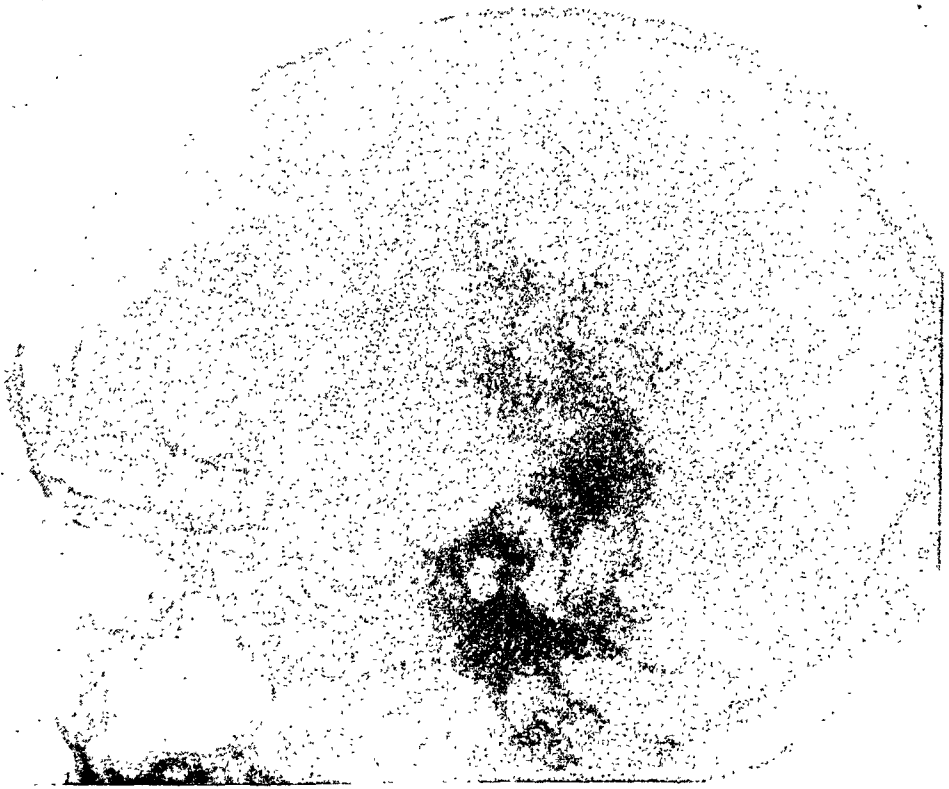


FIG. 7. Lateral roentgenogram of skull of case 19. Nineteen year old male, without preceding symptoms; examination made on date of auto accident. Type I of Moore.

tion can afford no understanding of the 50 per cent of female cases with hyperostoses who were shown by Moore⁴¹ never to have been pregnant. This point, of course, refers only to the etiological rôle of pregnancy, but does not exclude the ovary as a determining factor, though no characteristic ovarian pathology could be demonstrated by Henschen among patients showing *hyperostosis frontalis interna*. Ovarian involvement, possibly functional in nature, is suggested by the megalomastia characteristic of metabolic craniopathy and by the influence of follicular hormone on blood calcium, either directly, or by depression of the anterior pituitary gland function.

The relationship of hyperostosis and osteoma of the skull was suggested by Schneider, who, however, considered them separate entities, both dependent on dyspituitarism as a result of senile atrophy of the gland,⁶⁸ a relationship suggested by those cases of both entities associated with diabetes insipidus. He noted that osteomata were rarely accompanied by symptoms of brain pressure, whereas hyperostoses were frequently so characterized.



FIG. 8. Lateral roentgenogram of skull of case 7. Incipient frontal internal hyperostosis without symptoms in 13 year old son of case 4. Note patency of suture line.

The above theories of cause and development of the bony changes of metabolic craniopathy, although varied and ingenious, are inadequate to explain the total disease complex. This has been apparent to many writers, and Stewart⁷³ in 1928 first suggested dyspituitarism as the fundamental cause of hyperostosis. Morel⁴⁶ thought the adjacent tuber cinereum and infundibulum to be also involved, and Henschen reported hyperostosis

associated with pituitary pressure from adjacent meningioma. The investigations of Stewart, Moore, Casati, Carr, and others have demonstrated the intimate relationship of this disease to other endocraniopathies and have laid the foundation for its better understanding. It is at once recognized that the mechanical and inflammatory factors already discussed may be accessory modi operandi to such an endocrine pathogenesis.

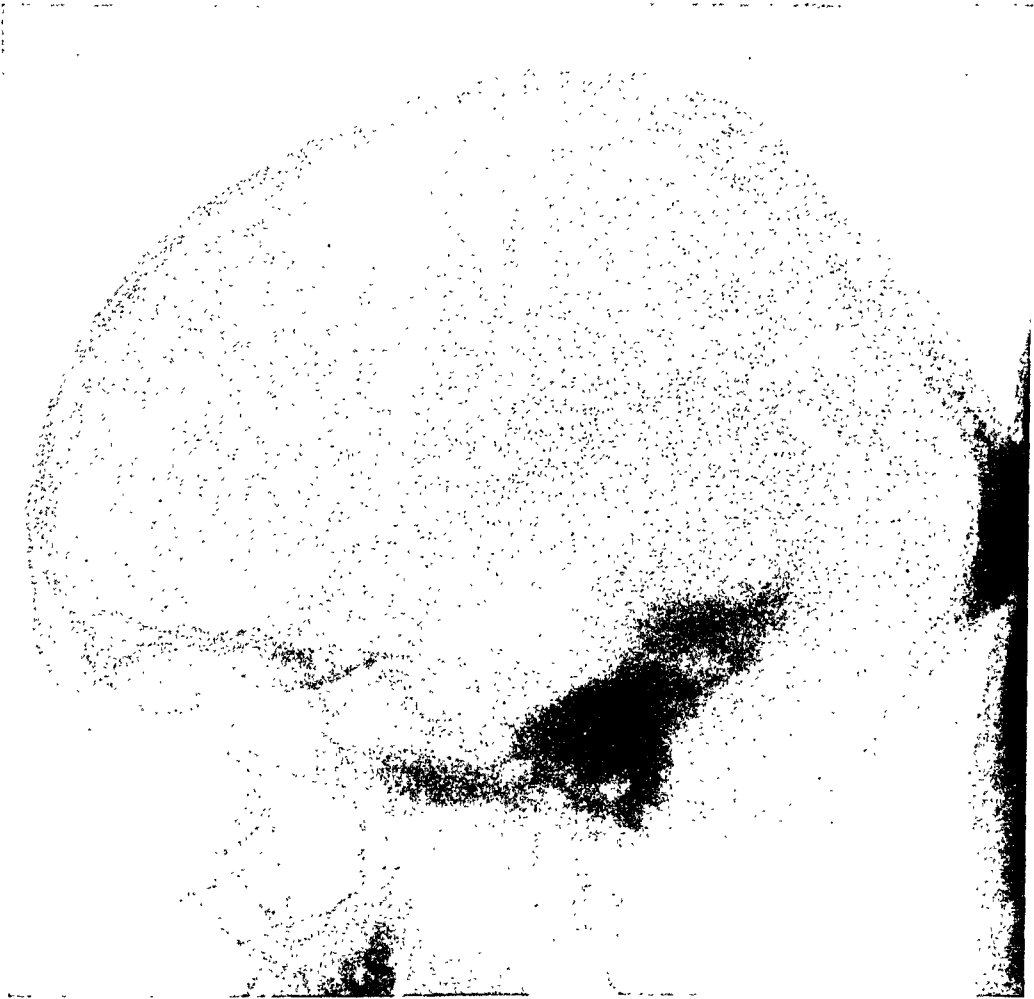


FIG. 9. Lateral roentgenogram of skull of case 6. Well-marked internal frontal hyperostosis in 16 year old daughter of case 4.

Such endocrine background of metabolic craniopathy appears at present well established. Thus, there have been associated with the disease true acromegaly and acromegaloid changes, with and without pituitary tumors.²⁵ Diabetes insipidus and certain features of the Froehlich syndrome have also been associated. Henschen²⁶ refers to the "pregnancy syndrome" with skull softening, new bone formation, acromegaloid changes and pituitary eosinophilia as a parallel instance of relation of the gland to bony changes.

Rutishauser, who is quoted by Henschen, referred to osteoporosis following hypophyseal basophilism. The Cushing syndrome of basophilic adenoma may show clinical features paralleling these of hyperostosis including the bony changes.



FIG. 10. Lateral roentgenogram of case 21. Tremendous internal frontal hyperostosis and calcification of falx. The deceptiveness of the lateral view is demonstrated in this instance by the antero-posterior picture which demonstrated that most of the frontal thickening here noted was due to the calcified falx. (See also figures 3 and 2.)

These pituitary changes involved in metabolic craniopathy may be considered to be:

1. Senescent.
2. Pre-senescent: (a) spontaneous, including degenerative and neoplastic lesions;
(b) Post-traumatic.

Extrapituitary influence has been invoked to explain the marked sex preponderance of hyperostosis. Stewart and Henschen incriminated the climacteric change of ovarian function, a view shared by Casati⁸ and suggested by the prominence of castration and menopause among patients with

the disease. Such a view is becoming less tenable, however, in view of the increasing number of preclimacteric and male cases reported, though in regard to the former it is recognized that menstruation may accompany early ovarian hypofunction. The influence of pregnancy, in spite of the suggestive bone changes noted by Henschen, is minimized by the 50 per cent of female patients with hyperostosis who have been nulliparous. Others have suggested an earlier senescence of the female as explanatory of the



FIG. 11. Lateral roentgenogram of case 27, showing hyperostosis frontalis interna, and circumscribed temporal osteoma.

preponderance,⁴¹ a view which appears inadequate to explain a 98 per cent proportion of cases. Mortimer has pointed out the generally hypopituitary state of the female as compared with the male, and found marked female preponderance among those pituitary dysplastic groups, which included the *hyperostosis frontalis interna*.

The possibility of an hereditary influence in determining the frontal localization of the bony changes by a modification of the appropriate gene

was suggested by Henschen. The possibility of the disease being due to sex-linked hereditary factor, possibly operating by pituitary determination, has apparently not been previously suggested, and the first reported evidence of such relationship is presented in our cases 4, 5, 6, and 7. The possible importance of such a factor in the pathogenesis of metabolic craniopathy



FIG. 12. Antero-posterior roentgenogram showing thickening of vault and temporal osteoma, case 27.

warrants its careful consideration and investigation in future instances of the disease, and may explain through endocrine growth control the localization, as well as occurrence, of the bony changes and metabolic abnormalities. Even if such a factor be proved by more detailed study, many other details of pathogenesis are yet to be determined. In fact, the exact source of the calcific tissue is not yet certain; various authors have placed the changes in

the diploë, the inner table, the outermost dural fibers, and the middle dural fibers. The determination of this point has been complicated by the varying involvement of all these structures in the pathological changes.

PATHOLOGY

Careful distinction must be made between pathological findings characteristic of and peculiar to this disease, and those often found associated with it incidentally, or as normal features of the age group involved. Thus, metabolic craniopathy is often found with senile generalized thickening of the skull, from which, however, it remains distinct.²⁵ The frequent references of Rokitanski to associated ivory-like exostoses of the skull, to cranial osteophytes, and to atrophy of other bones, including those of the face, again suggest that the author did not at times clearly distinguish metabolic craniopathy as it is now understood from other entities. Morel⁴⁶ and Pende⁵² described involvement of the frontal sinuses and sella turcica, a condition which has also been noted in other reports. Casati⁷ noted atrophy of the frontal lobes in psychopathic cases, while others³⁹ have been able to demonstrate no consistent changes in brain weights in even well-marked instances of the disease at autopsy.

Associated pituitary changes have been varied. Basophilic invasion of the neurohypophysis has been described,²⁵ as well as senile sclerosis of the anterior lobe. Reduction of the "head-cells" has occasionally been noted (Henschen²⁵), and also formation by eosinophiles of compact adenoma-like masses in the posterior part of the anterior lobe. Similar basophilic adenomatous masses in the lateral and anterior parts of the anterior lobe have been described by Henschen, and definite hypophyseal tumors have been reported, but he was able to demonstrate only normal senescent changes in the third ventricle and infundibulum. Morel described granular ependymitis of the third ventricle. He also found only normal senile changes in the ovary, and described associated pancreatic atrophy, lipomatosis, and infiltration of the parathyroid glands by acidophilic cells. No associated adrenal tumors have been reported.

Many of the aberrant physical findings of *hyperostosis frontalis interna*, including obesity, hirsutism, virilism, and others are obviously secondary to pituitary dysfunction, and as such bear a relationship to this disease, as they do to other diseases, such as pituitary basophilia, whose clinical picture they augment.

Thickening of the internal table is accomplished by the deposition of dense cancellous bone. Whether the osteoblastic cells are derived from the external or medial layer of the dura, from the internal table itself, or even from the diploë is not known. The degree of thickening is mainly dependent upon the amount of such deposition, which cannot be separated from the previously existent bone. In the adjacent diploë, condensation and actual increase in bony tissue at times occur, and constitute the most outstanding

features of Moore's second, third, and fourth groups. According to Mortimer this change results in a "lava-like" consistency of the diploë.

Changes in the hyperostoses during the period of observation have been described, though rarely. Two such progressive instances are described among the present series (cases 1 and 14). Osteoclastic activity has been described in excess of the osteoblastic changes especially in the frontal bones, resulting in Moore's group 5, though another explanation of such cranial thinning is offered by Mortimer. In all instances the dura is tightly adherent to the skull, a point important in consideration of surgery in treatment of the disease, as pointed out by Moore.

DIFFERENTIAL DIAGNOSIS

The typical changes of metabolic craniopathy are limited to the internal table and the diploë, resulting in diminished internal skull volume without external change other than a slight flattening of contour over the affected area in some advanced cases. Several otherwise confusable entities, including hemicraniosis, the prominent bosses of rickets, the olympic head of congenital syphilis, external osteomata and exostoses, and the bony changes of acromegaly, are at once eliminated by such criteria. Osteosarcoma is usually distinguished by its roentgen-ray appearance and speed of growth; metastatic carcinoma is similarly distinct. Dural endothelioma is usually unilateral and more localized than *hyperostosis frontalis interna*.

Osteomyelitis of the frontal bone may usually be recognized by its asymmetrical destructive and more rapid progress. A fibrous osteitis containing giant cells susceptible to roentgen-ray, especially in frontal and parietal bones with extension to malar and sphenoid areas, has been reported in young subjects.⁸ Localized Paget's disease and leontiasis ossea display characteristic extracephalic and facial changes. The compensatory bony overgrowth of the calvarium seen in senility is too generalized to cause confusion and lacks the typical topography at the internal table. Roentgen-ray appearances of calcific callus about fractures and of sequestra will rarely show confusing symmetry or location.

Localized syphilitic osteitis may be difficult to differentiate, for it may be rarefying or exuberant. An isolated frontal form is known in both congenital and acquired varieties,⁵⁵ but in all forms an irregularity of the lesion and predominant osteoclastic activity are distinctive. Similar features pertain to tuberculous osteitis.

The puerperal osteophyte^{24, 61, 14} has already been discussed under Pathogenesis, its differentiation being mainly one of definition. Osteitis deformans was carefully differentiated by Beadles.²

More difficult is differentiation of metabolic craniopathy on grounds other than the bony changes. Multiple sclerosis, paresis, and brain tumors, in relatively silent areas, may be confused with the clinical features of metabolic craniopathy unless recourse can be had to roentgen-ray. With

increasingly clear definition of the clinical picture of *hyperostosis frontalis interna*, however, it is inevitable that suspicion of the disease will more commonly precede roentgen-ray confirmation; this, in fact, has been reported.⁶⁰ It must even be considered possible, in view of the great inconstancy of every other feature, that the disease may exist occasionally without bony evidence. This is suggested by the experience of Rogers that several cases, symptomatically typical, lacked characteristic roentgen-ray findings of metabolic craniopathy.

SOCIAL ASPECTS

The social implications of any chronic disease are important, and all writers have emphasized the invalidism and even dementia associated with metabolic craniopathy. Incapacity for productive activity will result in long tenure of public support in many instances.⁴¹ Thus it is important that in Moore's series the average age at diagnosis was 44 years, and even then a preceding disability of variable length may be inferred. On the other hand, Greig found²⁴ the average age of death to be 70 years. If semblance may be assumed in the material reported, something like a half lifetime of dependency was experienced by the latter group of patients.

Literature points to but a single case of associated dementia with criminal violence, in the instance of a priest reported by Moreau⁴⁴ to have been executed for quadruple murder. Mental derangements more serious than irascibility or incompetence are otherwise rarely reported. In the present paper, however, the authors report the instance of a murderess with well-marked character changes complicating advanced *hyperostosis frontalis interna*. The occurrence may, of course, be entirely fortuitous, but the possibility of causal relationship must be kept in mind. Mortimer showed that 18 per cent of cases of cranial dysplasia, mainly of pituitary types, and including *hyperostosis frontalis interna*, were associated with emotional or mental abnormality. A third of these were under 17 years of age and had shown mental deficiency and behavior problems such as to merit institutional treatment. The social implications of these facts are obvious.

Remarkable variability and even consistent improvement in the clinical picture has been noted, as in two of our own cases, despite slight progression of the bony lesions during the period of observation. In general the constancy of the bony appearance is striking, and no retrogression of the lesions has been noted beyond the rarefaction in Moore's group 5. The contrasting great variability in the clinical picture from time to time is strong evidence of the independence of such factors from the bony changes. The average case of metabolic craniopathy has as its future only the status quo, or gradual progression, considering our present time of diagnosis and modes of treatment.

TREATMENT

Efforts at treatment have been restricted, of course, to the last eight years, since Morel's first report. In view of the associated marked muscular asthenia, aminoacetic acid has been administered with favorable results in some instances.⁶ In two of our own patients chondroitin has been administered (cases 1 and 4). Dosage varied from 40 to 60 grains daily. The results obtained appeared too dramatic to be lightly dismissed, and further investigation is warranted. Favorable changes have followed the use of phenobarbital, especially in instances of generalized spasticity and exaggerated tendon reflexes.⁶ Leri and Cottenot,³⁴ acting under an impression that the disease was of syphilitic origin, noted improvement following bismuth medication, an important commentary on the diagnostic value of therapeusis. Moore⁴¹ has suggested a rachitic diet in an attempt to restore a normal calcium balance, and, with Pende, suggested that parathyroid hormone might assist in the readjustment. The latter author reported no observable effect from such therapy, however. Large doses of vitamin B might be rational in consideration of the marked neuromuscular asthenia, and prostigmine should be tried in suitable instances. Ergotamine tartrate was used by Rogers and posterior pituitary extract by Pende, both with negligible benefit. Thyroid medication in view of the lowered basal metabolism was attempted in two cases of our own series with no observable effects after reasonable dosage.

Surgical decompression with removal of the most offending sections of bone has been suggested by several authors, but likewise not reported as accomplished. Its difficulty in view of the densely adherent dura is obvious. The probable success of surgical removal of the hyperostoses in controlling other manifestations of the disease is lessened by the apparent independence of the bone changes and other clinical features of the disease, as noted throughout this paper. Therapeutic pituitary radiation might afford relief in progressive cases, particularly of the headaches which are complained of by the majority of patients and which are not unlike those often experienced in menopause. Radiation of the frontal bone itself has been described by Pende; radiofrequency exposures have also been tried. Fever therapy used incidentally in one of our cases was without effect on the syndrome. The paucity of cases under actual observation by various authors has interfered with evaluation of therapeutic suggestions found in the literature, but, in view of the pathogenesis of the disease as recognized today, it is difficult to avoid a nihilistic attitude toward therapy other than that to be developed toward a correction of endocrine imbalances, probably in the early teens, certainly earlier than the usual age of diagnosis of metabolic craniopathy to date.

PRESENT SERIES OF CASES

Twenty-eight cases of *hyperostosis frontalis interna* are described in detail in the Appendix, and here reported for the first time. These consist

of 23 female and five male instances of typical metabolic craniopathy. Males are thus in greater proportion than has been noted in the summarized literature upon the subject, but clinically could in no way be distinguished from the female cases. Several previous authors have appeared to doubt the true nature of their male cases. Twenty-seven persons were white, and one colored; 19 were married, and nine single.

The average age of detection of the disease process in this group was 39.2 years; the oldest patient included was 67 years of age, the youngest 13 years. In general the average for the entire group is somewhat lower than that noted in any previous large series of cases. Greatest interest centers in the inclusion of five juvenile instances of the malady in three males aged 13, 19, and 19 years, and in two females aged 16 and 19 years. It is notable that in all these instances the bony changes were the principle findings, all other symptomatology remaining almost entirely latent. Three cases of these five were detected in the complete investigation of the family of a mother showing well-marked metabolic craniopathy, and were children who had been noted generally as being inept and retarded in school. Other than such ineptness no other complaints could be elicited. There is thus introduced an addition to the list of possible causes of childhood retardation, suggesting the advisability of skull roentgen-ray in such instances for the possible early detection of hyperostotic changes which may not yet have become irreversible. The two remaining juvenile patients were detected by roentgen-ray of the skull taken to determine the extent of injuries recently sustained in a fall and an auto collision respectively; no other previous complaints could be elicited. In both instances well-developed and unquestionable hyperostotic changes already were present. Time since the injury had, of course, been inadequate to permit any such sequelae to occur, but the rôle of an early ataxia or faulty judgment in causing the accident must be considered.

There are introduced then for the first time two features of importance to the concepts of cause and pathogenesis of *hyperostosis frontalis interna*. The clear-cut demonstration of its occurrence in three siblings and the mother of a single family, in cases 4, 5, 6, and 7, suggests a possible hereditary background, not only for the location of the bony changes, but also for the metabolic basis for their occurrence, possibly by means of pituitary determination and the inheritance of a pathological endocrine pattern. The possibility of hereditary determination of the frontal location of the outstanding bony changes of this disease was suggested by Henschen,²⁷ but no previous instance has been reported suggesting a familial basis for the occurrence of the disease. More extensive familial investigation will, of course, be required to establish the rôle of inheritance in this pathology.

The second point of interest in these five juvenile cases of definite *hyperostosis frontalis interna* with mainly latent symptomatology (cases 5, 6, 7, 11, and 19) lies in the demonstration of the early onset of bony changes, and

the precedence in time of such changes over the other clinical features of the disease in at least some cases. This fact has previously been suspected in, and further substantiated by those cases of the present series associated with trauma. Thus, 11 persons dated the onset of their symptomatology to a definite cranial injury. In six of these cases (2, 12, 22, 20, 25, 26), as in many in the literature, complaints seemed to begin immediately after the trauma and continued without interruption to the date of demonstration of cranial changes. It is upon such data that the rôle of injury in the production of the disease has been predicated in the past literature. In five other instances (10, 11, 15, 18, 19), however, in persons without previous cranial complaints and with none of the other usual criteria of metabolic craniopathy, well-developed bony changes were demonstrable upon skull roentgen-rays taken within 24 hours after cranial injury which was also followed by the onset of persistent headache, tinnitus, and the other usual features of the disease. In eight instances, therefore, of the 28 cases here reported bony changes preceded the onset of other clinical features of the syndrome. The dependence of the latter on the former is therefore challenged. It would appear more likely that both bony and functional changes, though mutually independent, might spring from a common, possibly heritable, endocrine dysfunction, or from one precipitated by trauma.

The clinical symptomatology of the cases reported herewith is not divergent from that noted in the literature. A headache usually, though not always, frontal, and described often as a boring pain was the outstanding symptom in 22 of the 28 cases. This was such a constant feature of the disease that the diagnosis of *hyperostosis frontalis interna* must be considered in the routine investigation of cephalalgia. It is usually intermittent, and in several instances was first noted following trauma. This, in view of the above demonstration of bony changes asymptomatic until injury, suggests the precipitating action of trauma in relation to the onset of the clinical syndrome, much as that of injury in relation to the pain of previously well-developed, but painless hypertrophic spinal arthritis, in which symptoms may be constant after trauma though never experienced before.

Vertigo, obesity, and mental changes were each reported in eight instances; tinnitus was noted in six persons. Four of the 23 females had had surgical or roentgen-ray ablation of the ovaries, and one had received depressant roentgen-ray therapy to the pituitary gland for the control of presumably menopausal headaches (case 28). The prominent occurrence of castration and of menstrual abnormalities among the female cases of the literature suggests the involvement of the ovary in the pathogenesis of the disease. Even if this ovarian involvement were demonstrable, it would, of course, not detract from the pituitary primacy. Weakness, memory loss, menstrual changes, and increase of the 24-hour volume of urine were each noted in three cases. An ataxia of a reeling, falling type, with marked unsteadiness of station and gait, was noted three times. Significant hyper-

tension and visual changes were each reported twice, and epileptiform convulsions were noted once.

In addition to the degenerative and mildly confusional mental picture reported commonly in the literature as complicating metabolic craniopathy an instance of homicidal psychosis was noted in case 12. This, with the case of the priest reported by Moreau, is suggestive of the potential social importance of the disease in addition to the economic loss represented by the prolonged debility and incompetence usually noted. In both of the now reported instances of murder, personality changes, quarrelsomeness, and incompetency in a person of previously high intelligence and responsibility preceded the violence. The possible rôle of this disease entity in the more violent psychosis of the age group commonly involved will, therefore, require more extensive investigation, while its importance in juvenile behavior disorders is suggested by the figures of Mortimer. These conclusions are supported also by Pende⁵² and others.

The associated pathology noted in the present series and not previously reported in the literature of the subject included carcinoma of the thyroid, with cranial metastases (case 23), and an instance of multiple myelomata with extensive cranial invasion including the sella turcica, but associated with unquestionable frontal internal hyperostosis and diabetes insipidus (case 28). Acromegaly was noted in one patient and acromegaloid changes in the facial skeleton and extremities of two others. An intracranial temporal osteoma was reported in case 27 in association with hyperostosis.

We have been unable to classify the roentgen-ray appearances of these cases as rigidly as suggested by Moore, and in many instances could not escape placing a given case in two groups. Thus of 28 cases, 23 showed Type I intracranial changes alone or principally, but four others showed it in lesser form, secondary to more marked changes of another type. Three cases showed primarily a diffuse thickening of the calvarium, or Type III change, but in five additional persons such thickening occurred with other more marked changes of other types. One Type II case was noted, but none of Type IV. The atrophic changes of Type V were demonstrable in three instances. It would appear, therefore, that any classification not admitting such overlapping would necessarily become arbitrary and artificial, and would require cautious application, especially as the clinical features of the disease are not proportional to the type of bony involvement.

Pre-roentgen diagnosis was attempted in several instances and was occasionally correct as shown by later pictures. This is in agreement with the experience of Rogers. The cranial changes yet remain the central criteria of the disturbances, and are likely to remain its most pathognomonic sign, at least if the entire entity does not become submerged into a larger endocrinopathic field with broader and more definite characteristics. The work of Mortimer has taken a long step in this direction.

SUMMARY

The important available literature of 173 years has been presented relative to a syndrome characterized in its fully developed form by numerous metabolic, endocrine, and neurological variations, with the common feature to date of bony skull changes of a symmetrical type, usually frontal in location. It is possible that even this common denominator may be slight, or absent in some cases as yet unclassified in the absence of a final understanding of etiology and pathogenesis of this syndrome. The opinions of many authors have been considered, and the data of the present paper are not at variance with preceding observations regarding the disease. It has been possible, however, to extend the concept of the malady, and to suggest additional factors relating to it. Mechanical, inflammatory, and even traumatic factors are generally recognized today as secondary to an endocrine background. Most writers have linked the disease with the pituitary gland and occasionally with the ovarian changes of the menopause, in consideration of the average age of detection of the disease. In view, however, of the younger ages of detection reported in occasional papers on the subject, and the five cases in the present paper under 20 years of age, or eight under 30, it has become apparent that the age of pathogenesis may long precede menopause. In all, seven instances under 20 years of age have now been reported in the entire literature, including the five cases in the present series. A similar doubt of menopausal effect is cast by the now not inconsiderable number of male cases reported in the literature, including five of the present series. It is difficult, however, not to accord to the ovary some rôle, possibly secondary, in pathogenesis, through a depressant effect on anterior pituitary activity, with in turn an effect on calcium metabolism, a vicious circle being thus established.

Three of the juvenile cases here reported (cases 5, 6, and 7) were siblings of a mother with well developed frontal hyperostosis (case 4), suggesting a familial and possibly an hereditary basis for the disease. This possibility had already been suggested by Henschen in regard to the frontal localization of the bony changes, but so far as we are aware these cases constitute the first evidence of such background for the disease itself. If it be a change predominantly sex-linked, its sex preponderance may require no additional explanation. It is readily admitted, however, that the instances noted herewith are merely suggestive rather than conclusive evidence of such relationship. The usual discovery of the disease at later ages may depend upon slowly progressive changes, beginning much earlier with secondary changes of more imperative nature leading to detection later. The discovery of well-marked hyperostosis in traumatic cases without previous symptoms suggests a possible long period of latency. In view of the very slight impairment of general physical health in the earlier stages, it is obvious that the majority of pathological studies have been made late in senile patients, overlooking the younger cases.

The endocrine aspects of the disease appear unquestionable and are, in fact, quite compatible with an hereditary concept of pathogenesis, of which they may represent the mechanism underlying these changes.

In the present paper a progression of cranial changes has been reported during periods of observation of two patients, including not only the diploic changes reported by previous writers, but also change of the frontal internal hyperostosis. Extracranial changes are, however, rare.

The association with history of trauma appears at first too definite to be denied, and it is probable that in some instances pituitary or adjacent changes have been induced by injury to the head, which have ultimately resulted, through secondary endocrine mechanisms, in hyperostosis and other features of metabolic craniopathy. In many other cases, however, it is obvious that injury has served only to bring to light previously latent, asymptomatic changes, which thereafter became and remained notable.

The social implications of this disease are important in view of the high morbidity at potentially highly productive life periods. The length and intensity of such disability rank the disease with permanent functional insanity in terms of disaster to the patient. Three instances of violent anti-social tendencies have been reported, including a patient with "revenge psychosis" and two murderers, one reported herein. In most instances, however, the psychoses have been mild, and have tended to be intermittent. Thus this disease assumes a further importance in consideration of the background of psychoses of hitherto uncertain etiology, as demonstrated by Moore.

Treatment to date has been variable, and mainly symptomatic or empirical. It has generally been ineffective, and the occasional measures reported as successful must be more widely applied under careful observation and over longer periods of time before proper evaluation is possible. In view of our concepts of pathogenesis surgical removal of the hyperostoses, difficult in view of the dense dural adhesions, would probably not be either feasible or effective. It has been demonstrated that the clinical features of the cases are not always directly dependent on the type or extent of bony changes involved, and are often dissociated in terms of time element. The surgical approach should, therefore, be conservatively considered. It is desirable that future reports should include critical analyses of the treatments used in a disease generally so debilitating, as well as careful investigations of the familial background of the patients.

We are indebted to Dr. John V. Horst for his permission to include in our series Cases 4, 5, 6, and 7, so important to our concepts of the disease.

CASE REPORTS

Case	Age	Sex	Race	Married	Epitome
St. F. (1)	66	F	C	S	Vertigo, frontal headache, ataxia, propulsion, retropulsion, loss of memory, tinnitus, coarse intention tremor, and paresthesia of hands and arms, all of sudden onset, suggesting cerebral vascular accident, four weeks before admission. Moderate obesity, negative serology and spinal gold curve of 1112200000. Roentgen-ray of typical hyperostosis frontalis interna. (Type I, figures 3, 4, and 5). Treated by phenobarbital .09 gm. and chondroitin 4 gm. daily with improvement permitting domestic engagement. Recheck in 18 months shows all symptoms markedly improved, slight increase of intracranial lesions, thickening of diploë, and flattening of external contour of skull. Moderate hypertension.
St. F. (2) 37-157	45	F	W	S	Vomiting at menstruation from onset at 13 until hysterectomy at 32. Headache recurrent since pneumonia at 29, with tinnitus, partial deafness, and occasional vomiting, fatigability, frequency, polyuria, obesity, blood pressure 192/134, hirsutism, insomnia, vertigo, intention tremor, weakness, multiple neuralgias, and dryness of skin; tenderness 2 inches above glabella. Momentary unconsciousness, followed by retropulsion, after head injury at 41, with accentuation of all symptoms. Roentgen-ray showed corrosion of frontal bone 1 inch above sinuses with surrounding hyperostotic changes (Type I). Serology negative. Death 48 hours after removal of subdural hematoma. Particular interest lies in development of clinical stigmata of metabolic craniopathy nine years before trauma responsible for hematoma.
St. F. (3) 37-150	26	F	W	S	Recurrent vertigo and band-like headaches for eight months following menorrhagia of 75 days with recent sudden obesity. Basal metabolism minus 15. Roentgen-ray typical of early frontal hyperostosis (Types III and I). Clinically unimproved by desiccated thyroid.
J. H. Mrs. G. T. (4)	41	F	W	M	Unilateral ovariectomy at 37 followed by mild menopausal syndrome, menstrual irregularity, headache, vertigo, recurrent nervousness, drowsiness, lack of concentration, poor memory, male hirsutism, and moderate obesity. B.P. 104/64. B.M.R. minus 7. Roentgen-ray changes showed typical internal frontal hyperostoses. (Types I and II). Returned to care of household on desiccated thyroid 0.2 gm. and chondroitin 2.6 gm. daily with weight loss and subsidence of complaints to occasional headache.
J. H. (5)	19	M	W	S	Son of case 4, showing notable mental sluggishness, and retardation in school; no complaints. Roentgen-ray showed slight roughening of inner table of frontal bone (Type I).
J. H. (6)	16	F	W	S	Daughter of case 4, with mental retardation and appearance of mild hypothyroidism. Roentgen-ray showed well advanced internal frontal hyperostosis (Type I, figure 9).

Case	Age	Sex	Race	Married	Epitome
J. H. (7)	13	M	W	S	Son of case 4, investigated in routine family survey. No complaint. Definite frontal hyperostosis limited to frontal table (Type I, figure 8).
U. H. 361512 (8)	62	F	W	M	Left facial neuralgia of two years' duration, without paroxysms or trigger zone, after respiratory infection with tinnitus and left epiphora, unrelieved by temporomandibular injection. Garrulous, with personality changes. 11 pregnancies, two miscarriages; hysterectomy at 35. Gallbladder colic at 61. B.P. 140/90; moderate obesity; serology normal. Roentgen-ray showed moderate hyperostosis (Types I and II). Unimproved after fever therapy by typhoid vaccine and radiofrequency hypertherm.
U. H. 382547 (9)	47	F	W	M	Frontal headaches with vomiting for five years. Development of frontal and hard occipital masses within two years. Nervousness for several years, with recent persecutory psychoses and visual hallucinations. Progressive acromegalic changes for two years, with enlargement of feet and hands, and exostoses in frontal area and behind left ear. Roentgen-ray menopause at the age of 42. B.M.R. minus 6. Serum calcium 9 mg. per cent. Roentgen-ray showed frontal hyperostosis interna and diffuse thickening of the entire skull (Types II and IV, figure 6). Treated by roentgen-ray of pituitary without improvement.
W. C. 164 (10)	58	F	W	M	Routine examination immediately after auto accident. Five pregnancies; menopause at 42; hypertensive; very obese. Roentgen-ray showed well marked frontal hyperostoses (Type I). No previous complaints.
W. C. 4400 (11)	19	F	W	S	Examined 12 hours after occipital head injury which was followed by frontal aching; no preceding symptoms. Roentgen-ray showed well marked internal frontal hyperostoses (Type I). Student nurse; physical characteristics not remarkable.
H. L. Mrs. M. H. (12)	39	F	W	M	One pregnancy, one child dead of muscular dystrophy. Above average intelligence, complaining of irritability, depression, emotional instability, carelessness, vertigo, staggering gait, fatigability, and memory loss of two years' duration. Recent discharge from position because of incompetence. Sudden menopause at 38. Constant head pain since kicked by horse at the age of 25. B.P. 124/60. Serology normal. Committed murder; found insane. Roentgen-ray showed skull thickened throughout, except in posterior-occipital areas; depression with fracture lines in left lateral frontal area. Calcification of falx cerebri and hyperostosis frontalis interna, more marked on left (Types I and II, figures 1 and 2).
S. C. O. P. Mrs. W. W. (13)	60	F	W	M	Complaints of headache and obesity of long duration. Roentgen-ray demonstration of nebula frontalis and slight internal hyperostoses (Types I and II).
W. C. 375-221 (14)	53	F	W	M	Brain tumor suspect with frontal headache of several hours' duration every two to three days. Obese. Serum calcium 12.1 mg. per cent. Roent-

Case	Age	Sex	Race	Married	Epitome
					gen-rays of 7/19/37 show wide vascular channel in parietal bone to midline of vault where there are several areas of decreased density; slight frontal hyperostoses. All abnormalities slightly increased at repeated study 9/30/37. Definite increase in hyperostoses and diminished rarefaction 11/3/37 (Types V and I).
W. C. 3467 (15)	31	F	W	M	Examined several hours after auto accident for continuing headache; no previous complaints. Forehead laceration. Roentgen-ray showed well marked internal frontal hyperostoses (Type I).
W. C. 295 (16)	30	F	W	S	Investigation because of headaches. Serology negative. Roentgen-ray shows incipient frontal internal hyperostoses (Type I).
W. C. 1829 (17)	67	M	W	M	Serology negative. Roentgen-ray showed well marked internal frontal hyperostoses (Type I) in routine investigation of headaches.
W. C. 188 (18)	22	F	W	M	Head pains persistent after momentary unconsciousness in auto accident of date of examination. Five months' gravid. Frontal hematoma, nasal hemorrhage, ecchymoses about left eye. Early hyperostosis frontalis interna and fractures of left frontal bone revealed by roentgen-ray (Type I).
W. C. 4443 (19)	19	M	W	S	Examined on date of injury by auto; no unconsciousness, but persistent right parieto-occipital pain. Left pupil dilated but reactive to light. Roentgen-ray showed marked wave-like internal frontal hyperostoses (Type I, figure 7).
U. H. 366-995 (20)	30	F	W	M	Head pains radiating from right mastoid area beginning three months after fall on right parietal area one year before examination; no unconsciousness or laceration. No previous symptoms. B. P. 126/74. Wt. 125 lbs. A tender two-inch depression behind right ear. Serology and all other physical examinations normal. Roentgen-ray and encephalography showed osteoporosis in right parietal area and vertex; hyperostosis frontalis interna; plastic arachnoiditis, right midparietal area (Types V and II).
H. L. Mrs. E. J. (21)	34	F	W	M	Failing vision for one year, slightly improved after dental extraction, with recent vertigo, weakness, staggering gait, urinary retention, tinnitus, with periods of dizziness, and menstrual irregularity during past year. Roentgen-ray showed marked calcification of falx cerebri and tremendous frontal internal hyperostoses (Type I, figure 10).
W. C. 380-035 (22)	33	F	W	M	Recurrent incapacitating head pains radiating from left frontal area to occiput, with periods of vertigo and nervousness since unconsciousness of 30 minutes' duration after striking head on beam five years previously; bilateral salpingectomy and unilateral ovariectomy three years before injury. Examination negative except for absent Achilles reflex. Roentgen-ray showed mild internal frontal hyperostoses (Type I).

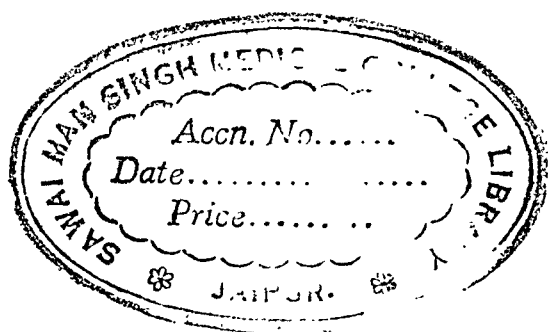
Case	Age	Sex	Race	Married	Epitome
St. F. 37-1216 (23)	62	F	W	M	Removal of non-toxic nodular goiter 10 years previously, with growth in last five months of firm mass in area of left lateral thyroid lobe, weight loss, and development of a left frontal mass with bruit and thrill. Serology normal. B.P. 150/90. Retinal veins slightly distended. Roentgen-ray of skull shows symmetrical hyperostosis frontalis interna with unilateral two-inch erosion without regeneration in area of left frontal bone (Types I and II). Long bones showed osteoporosis. Biopsy showed thyroid carcinoma metastatic to skull.
P. T. K. A. M. (24)	24	F	W	S	Convulsive seizures of increasing frequency during 18 months, followed by nausea, vomiting, occipital head pain, prostration. Onset of right supra-orbital pain in last month. Juvenile goiter at the age of nine, with persistent slight enlargement, Wt. 122 lbs. B.P. 128/60. B.M.R. minus 6; serology normal; menstrual history normal. Roentgen-ray showed moderate internal frontal hyperostoses (Types I and V) and rarefaction at lateral extremity of right supraorbital ridge. "Typhoid fever" diagnosed 18 months before onset associated with marked headache. Anterior horns of lateral ventricles shown by encephalography to be dilated.
W. C. 373-486 (25)	51	F	W	M	Frontal and bregmatic headaches, sense of weight on top of head, vertigo, and unsteadiness resulting in several falls since blow on head with unconsciousness of 20 minutes' duration five years previously. B.P. 160/95. Obesity moderate. Serology negative. Roentgen-ray showed no evidence of fracture, but moderate internal frontal hyperostoses (Type I).
W. C. 373-997 (26)	37	M	W	M	Recurrent severe occipital head pain since struck by slate slide two years previously. Tinnitus in right ear since mastoidectomy 11 years previously, Weber test referred to right; right bone conduction better than air conduction. B.P. 140/94. Anesthesia of mandibular branch of left fifth nerve. Serology negative. Roentgen-ray showed moderate internal frontal hyperostoses and sphenoid and maxillary cloudiness (Type I).
U. H. 354375 (27)	42	F	W	M	Five years of progressive pain and drawing sensation at vertex, with deafness, tinnitus, vertigo, and failing vision. Mass in inner left temporal table demonstrated by roentgen-ray two years before. Sagittal suture had remained open until the age of five years, and was now marked by prominent bony ridge. Deficient mentality. B.P. 140/90. Left second and eighth cranial nerves impaired. Roentgen-ray showed well-defined temporal osteoma and hyperostosis frontalis interna. The first was removed surgically, with disappearance of discomfort and tinnitus (Type I, figures 11 and 12).
U. H. 386-488 (28)		F	W	M	Moderately obese, with 15 years' weakness, polydipsia, polyuria, and occasional glycosuria without elevation of blood sugar. B.P. 124/75. Roentgen-ray demonstration of multiple myelomata indicated by bone marrow studies. Moderate degree of frontal internal hyperostosis (Type I). Posterior pituitary lobe extract without effect on headache, but with relief of polyuria during administration.

BIBLIOGRAPHY

1. ALMQUIST, R.: Stewart-Morel syndrome, *Acta psychiat. et neur.*, 1933, viii, 279-287.
2. BEADLES, C. F.: The cranium of the insane, *Edinburgh Med. Jr.*, 1898, iii, 263.
3. LEWIS, BEVAN: Textbook of mental diseases, 1889, London.
4. BIRKET, J.: On cartilaginous and bony growths, *Guy's Hosp. Rep.*, London, 1869, 3rd serv., xiv, 493.
5. BONNAMOUR and JAMIN: *Maladie Osseuse de Paget au Niveau de Crane*, *Lyon méd.*, 1926, cxxxviii, 535.
6. CARR, A. D.: Neuro-psychiatric syndromes associated with hyperostosis frontalis interna, *Arch. Neur. and Psychiat.*, 1936, xxxv, 982-989.
7. CASATI, A.: Die senilen Schädelveränderungen im Roentgenbild, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, Hamburg, 1926, xxxiv, 335-342.
8. CASATI, A.: Internal hyperostosis, a case, *Radiol. med.*, 1936, xxiii, 625-632.
9. CHIARI, H.: Zur Kenntnis der senilen grubigen Atrophie an der Aussenfläche des Schädels, *Virchow's Arch. f. path. Anat.*, 1912, ccx, 425.
10. CLAUSTON, T. S.: Clinical lectures on mental diseases, Fourth Ed., 1898, London, p. 733 and Plate VI.
11. DAKIN, W. R.: A handbook of midwifery, 1897, London, p. 57 (quoted by Greig).
12. DELEE, J. B.: The principles and practice of obstetrics, 1913, W. B. Saunders Co., Philadelphia, p. 104.
13. DIETZ, W. G.: Weitere Beiträge zur secundären konzentrischen Hyperostose am Schädel, 1908, Wurzburg (quoted by Morel ⁴⁶).
14. DORLAND, W. Z. N.: A manual of obstetrics, 1896, Philadelphia, p. 78.
15. DRESSLER, L.: Hyperostosis of the frontal bone, *Beitr. z. path. Anat. u. z. allg. Path.*, 1927, lxxviii, 332-363.
16. DREYFUSS: Halban-Seitz, *Kehrer* vi, 2, p. 2.
17. EISEN, B.: The internal frontal hyperostosis syndrome, *Can. Med. Assoc. Jr.*, 1936, xxxv, 24-27.
18. FELDMAN, E. A., and SALOVEY, Y. V.: Syndrome of internal frontal hyperostosis, *Urach. delo*, 1938, xx, 17-20.
19. FOLLIN, E., and DUPLAY, S.: *Traité élémentaire de pathologie externa*, Paris, 1874, iii, 577.
20. FRACASSI, T., and MORELLI, F. L.: Internal hyperostosis, four new cases, *Rev. argent. de neur. y. psiquiat.*, 1936, ii, 65-67.
21. FUCHS, A.: Changes of the cerebral dura mater in cases of increased intracranial pressure, *Arb. a. d. neur. Inst. a. d. Wien. Univ.*, 1933, x.
22. GALABIN, A. L., and BLACKER, G.: The practice of midwifery, 1910, The Macmillan Co., London, p. 168.
23. GIANTURCO, C.: Report of autopsy, 1930 (quoted by Casati ⁸).
24. GREIG, D. M.: On intracranial osteophytes, *Edinburgh Med. Jr.*, 1928, xxxv, 165-191, 237-260.
25. HENSCHEN, F.: Morgagni syndrome, *Hygeia*, 1936, xcvi, 65-85.
26. HENSCHEN, F.: Morgagni syndrome, *Ann. d'anat. path. méd.-chir.*, 1936, xiii, 943-960.
27. HENSCHEN, F.: Hyperostosis verrucosa frontalis interna and its significance, *Acta path. et microbiol. Scand.*, 1936, Supp. xxvi, 95-97.
28. HOWSHIP, J.: Practical remarks on the discrimination and appearances of surgical disease, 1840, London, p. 330.
29. HUMPHREY, G. M.: Senile hypertrophy and senile atrophy of the skull, *Med. and Chir. Trans.*, 1890, London.
30. KOCK, M.: Demonstration of cranium with Paget's osteitis deformans, *Verhandl. d. deutsch. path. Gesellsch.*, 13, Tagung 1909.
31. JAMES, T. G. I.: Hyperostosis frontalis interna, *Brit. Jr. Radiol.*, 1936, ix, 750-752.

32. LEGUEST, and SERVIER: Museum specimens, Dictionaire Encycl. des Sci. méd., 1879 quoted by Morel ⁴⁵).
33. DE LEHOCZKY, T., and ORBAN, A.: Hyperostosis frontalis interna, Brit. Med. Jr., 1938, i, 1049-1050.
34. LERI, A., and COTTENOT, P.: Radiodiagnostic de la syphilis tardive ou hereditaire, Les osteitis de la stalbe interne de crane, Presse méd., 1926, xxxiv, 801.
35. LERI, A., and LIEVRE, J. A.: Fronto-parietal craniostosis in a child with Little's disease, Arch. de méd. d. enfants, 1928, xxxi, 669-675.
36. LEVISON, P.: Morgagni syndrome, Hospitalstidende, 1937, lxxxi, 352-354.
37. LOBSTEIN, J. F.: Traité d'anatomie pathologiques, Paris, 1833, ii, 140 (quoted by Greig ²⁴).
38. LOESCHKE, L., and WEINOLDT, H.: The influence of pressure and relaxation on the growth of the skull, Ziegler's Beitr., 1922, lxx, 412.
39. MARCHAND, F.: The weight of the human brain, Abhdlg. d. math. phys. Klassa der Kgl. S. Ges. d. Wissensch., Bd. 27, Nr. iv, 436.
40. MEYER, H.: Zur Frage der sekundären Konzentrischen Hyperostose der Schädelknochen bei Volumenabnahme des Hirns, 1908, Wurzburg (quoted by Morel ⁴⁶).
41. MOORE, S.: Hyperostosis frontalis interna, Surg., Gynec. and Obst., 1935, lxi, 345-362.
42. MOORE, S.: Calvarial hyperostosis and the accompanying symptom complex, Arch. Neur. and Psychiat., 1936, xxxv, 975-981.
43. MOORE, S.: Metabolic craniopathy, Am. Jr. Roentgenol. and Radium Therap., 1936, xxxv, 30-39.
44. MOREAU, M.: Crimes committed by Jacques Pierlot, priest; probable rôle of Stewart-Morel syndrome in causing mental changes, Jr. Belge de Neur. et Psychiat., 1934, xxxiv, 458-463.
45. MOREL, F.: Hyperostosis frontalis interna, 1930, Gaston, Doin, and Cie, Paris; 1930, Geneva.
46. MOREL, F.: Hyperostosis frontalis interna, Schweiz. med. Wchnschr., 1937, lxxvii, 1225-1248.
47. MORGAGNI, J. B.: De Sedibus et Causis Morborum, Lib. II, Epistl. xxvii, 1765, Padua.
48. MORTIMER, H.: Arch. Neur. and Psychiat., 1936, xxxv (in discussion of Carr's paper ⁶).
49. MORTIMER, H., LEVENE, G., ROWE, A. W.: Cranial dysplasias of pituitary origin, Radiology, 1937, xxix, 2, 135-157, and 279-290.
50. NAITO, I.: Die Hyperostosen des Schädels, 1924, J. Springer, Vienna and Leipzig, p. 18 (quoted by Dressler ¹⁵).
51. NAITO, I., and SCHULLER, A.: Über die Hyperostosen des Schädels, Wien. klin. Wchnschr., 1923, xxxvi, 794.
52. PENDE, N.: Krankheitsbilder b. Veränderungen des Schädelinners, München. med. Wchnschr., 1937, lxxxiv, 855.
53. PERKINS, O. T., and BIGLAN, A. N.: Hyperostosis frontalis interna, Psychiat. Quart., 1938, xii, 341-350.
54. PICARD, P.: Epaississement Pagetique de Crane avec Syndrome Démentiel, Bull. Soc. clin. de méd. ment., 1926, Nov.-Dec.
55. PROBY, H.: L'osteite syphilitique de Crane et de l'os frontale, Ann. d'oto-laryngologie, 1933, ii, 1290-1307.
56. REDAELLI, P.: Report of autopsy, 1931 (quoted by Casati ⁸).
57. REICHARDT, M.: The bone changes in progressive paralysis, Zentralbl. f. Nerven. u. Psychiat., 1906, xxix, 705 (quoted by Dressler ¹⁵).
58. REIDER, N.: Alzheimer's disease associated with hyperostosis frontalis interna, Bull. Menninger Clin., 1937, i, 123-128.
59. RIBERT: Textbook of general pathology and pathological anatomy, 6th Ed., 1919, Leipzig, p. 768 (quoted by Dressler ¹⁵).
60. ROGERS, A. A.: Internal frontal hyperostosis syndrome, Can. Med. Assoc. Jr., 1938, xxxviii, 129-132.

61. ROKITANSKI, K.: Manual of pathological anatomy (Sydenham Soc. Trans.), 1850, London, iii, p. 130.
62. ROKITANSKI, K.: Handbook of anatomical pathology, 1842, Vienna, ii, pp. 142, 236, 242.
63. SAUVAGE, H. E.: Note sur l'état senile du Crane, Bull. Soc. d'Anthropol., Paris, 1870, ix,
64. SCHACHTER, M.: Morgagni syndrome, Gaz. d. hôp., 1937, cx, 1453-1456.
65. SCHIFF, P., and TRELLES, J. O.: Hyperostosis frontalis of traumatic origin, Ann. de méd. lég., 1932, xii, 10-14.
66. SCHLESSINGER, H.: Die Krankheiten des höheren Lebensalters, Nothnagel's spezielle Pathologie du Therapie, Suppl. Vol. VIII and IX.
67. SCHMIDT, M. B. in Aschoff: Pathol. Anat. II (quoted by Dressler ¹⁵).
68. SCHNEIDER, E.: Cranial osteoma and hyperostosis frontalis, Med. Klin., 1936, xxxii, 487-490.
69. SHATTOCK, S. G.: Case report, Internat. Med. Congr., 1913, viii, 2, 26-32.
70. SIPPEL, A.: Zur Actiologie des Exostosen u. Osteome am Schädel, 1909, Wurzburg (quoted by Morel ⁴⁰).
71. KNAGGS, L.: Inflammatory and toxic diseases of bone, 1926, Bristol.
72. SOMOGY, I., and BOK, R.: Über d. neuro-psychiatrischen Beziehungen d. Schädelhyperostosen, Deutsch. Ztschr. f. Nervenhe., 1937, cxliii, 199.
73. STEWART, R. M.: Localized cranial hyperostosis in the insane, Jr. Neur. and Psychopath., 1928, viii, 321-331.
74. STROEBE, S.: Handbuch der pathologischen Anatomie des Zentralnervensystems, 1904, Berlin, pp. 314-315.
75. STUTZ, G.: Hyperostosis frontalis interna in a case of presenile dementia, Arch. f. Psychiat., 1934, ci, 798-799.
76. SUSSE, K.: The problem of concentric hyperostosis of the frontal bones, 1908, Wurzburg (quoted by Morel ⁴⁰).
77. TERRIER, F., and LUC, H.: Manifestations tardives de la syphilis chez les Vieillards, Rev. de chir., 1881, i, 103.
78. THOMA, R.: Research concerning bone formation and its disturbances, Virchow's Arch. f. path. Anat., 1917, ccxxiii, 33.
79. VANBOGAERT, L.: Syndrome of hyperostosis frontalis, Jr. de Neur. et de Psychiat., 1930, xxx, 502.
80. WILKES, S.: Puerperal osteophytes in the calvarium, Trans. Path. Soc. London, 1857, viii, 317.
81. WILLIAMS, J. W.: Obstetrics, Fifth Ed., 1923, New York, p. 197.
82. ZANDER, R.: Monograph on the dura mater and bone development, Festschrift zur 70 Geburtstag von Karl von Kupffer, June, 1899.



THE RÔLE OF DIABETES IN THE DEVELOPMENT OF DEGENERATIVE VASCULAR DISEASE: WITH SPECIAL REFERENCE TO THE INCIDENCE OF RETINITIS AND PERIPHERAL NEURITIS *

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THE advent of arteriosclerosis is one of the inevitable consequences of aging. The existence of arteriosclerosis in one or another part of the vascular tree after the age of 30 is to be expected. Its rate of progression and its predilection for certain special arterial channels are factors which influence profoundly the problem of longevity. It is apparent, also, that the anatomic distribution of the sclerotic process in relation to the arterial wall itself is an important consideration in determining the seriousness of the disease. Thus, the intimal lesion affecting the medium-sized muscular arteries (coronary, cerebral and tibial) gains special prominence because of the likelihood of formation of secondary thrombi, with diminution and later obliteration of the lumens of such medium-sized muscular arteries. Neither the Mönckeberg type of sclerosis nor, indeed, the intimal lesions of the larger elastic arteries possess the same potentialities for vascular occlusion.

There are no doubt many factors which may influence the rate and extent of arteriosclerosis but our knowledge is, at best, inadequate to explain the phenomena which initiate arteriosclerosis or those which accelerate its progress. The one factor which has received widespread consideration as a contributory cause to arteriosclerosis is diabetes mellitus. The recent survey of the incidence of coronary sclerosis among diabetic and nondiabetic patients carried out by Root, Bland, Gordon and White¹ again emphasizes this fact. The postinsulin era offers especially valuable subject material for analysis. Indeed, the introduction of insulin has created a fascinating biologic experiment, inasmuch as the diabetic patient now lives longer not only with his diabetes but also with his arteriosclerosis.

POSSIBLE ERRORS IN THE APPRAISAL OF THE EFFECT OF DIABETES ON ARTERIOSCLEROSIS

At the outset, we must recognize certain obstacles to the accuracy of a survey which is intended to reflect the effects of diabetes on arteriosclerosis.

The first of these obstacles is the personal equation in the estimation of the degree of arteriosclerosis present, inasmuch as there is no clear-cut distinction separating what might be termed "physiologic" from "pathologic" arteriosclerosis.

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The second obstacle is the question of the availability of sufficient data to satisfy statistical requirements, as well as the question of the correct interpretation of such data. One of the most common errors committed in the appraisal of arteriosclerosis in the presence of diabetes arises out of a direct comparison of data pertaining to diabetic subjects with data pertaining to nondiabetic subjects, without reference to the relative incidence of the two conditions. Since the general population contains about 100 times as many nondiabetic patients as it does diabetic patients, the data secured from this type of direct comparison can in no way reflect the facts accurately.

The third obstacle is the question of selecting a division of the arterial tree which lends itself to the study of its functional integrity. Most studies of this type have centered around the coronary circulation, but in a study of the coronary circulation the obstacles to accuracy are far from negligible. If clinical material is used, it must be recalled that coronary disease may be strikingly latent in the presence of diabetes (perhaps because of the hyperglycemia present in such a condition) and electrocardiographic evidence may be misleading because both hypertension and diabetic acidosis may produce changes simulating those changes incidental to coronary sclerosis. If data pertaining to observations made at necropsy are preferred, the problem arises of availability of a sufficiently large series of cases to satisfy statistical requisites.

NATURE AND SCOPE OF THE PRESENT STUDY

The present study deals with the incidence and the complications of occlusive peripheral arteriosclerosis among diabetic and nondiabetic patients, and with certain phenomena frequently associated with arteriosclerosis among diabetic individuals. The study has been carried out with the authors being fully cognizant of the difficulties previously detailed, and an attempt has been made to overcome these difficulties as far as is possible.

Thus, we selected the peripheral arterial system for study because it permits of the use of clinical material. In so doing, the question of the personal equation in the appraisal of the degree of arteriosclerosis present in individual arterial channels is obviated. The central problem, after all, is not merely the existence of arteriosclerosis. That is assumed to be present. The central problem is whether the functional integrity of the arterial system, in the region of the body under consideration, is or is not intact. The phenomena characterizing arterial insufficiency in the peripheral circulation, both subjective and objective, happen to be reasonably clear-cut: claudication, coldness, ischemic neuritis, excessive pallor on elevation and excessive rubor on dependency, absent pulsations, trophic changes of the nails and, in its extreme form, trophic ulcers and gangrene. Forms of obliterating arterial diseases from causes other than arteriosclerosis can be differentiated usually without difficulty. A special effort was made in our group to make this differentiation. The selection of this particular field, moreover, offers a

far wider scope for analysis than does the selection of any other part of the arterial system.

Finally, the errors inherent in statistical analyses have been obviated in so far as the Division of Biometry and Medical Statistics of The Mayo Clinic has placed at our disposal the necessary control data, consisting of the total number of patients (both diabetic and nondiabetic) in each decade, examined at the clinic during the yearly periods corresponding to our study.

Material. 1. The diabetic group contained 230 diabetic patients (of a total number of 7,073 diabetic patients examined consecutively at the clinic during the years 1928 to 1938, inclusive) representing all patients presenting clinical evidence of the existence of arterial insufficiency of varying degrees in the lower extremities, and thus permitting of a diagnosis of occlusive peripheral arteriosclerosis.

2. The control group, or nondiabetic group contained 219 nondiabetic patients (of a total number of 197,894 nondiabetic patients examined consecutively at the clinic during the years 1929 to 1933, inclusive) representing all patients for whom the diagnosis of occlusive peripheral arteriosclerosis was made. The criteria for determining the presence and the degree of arterial insufficiency were the same in both groups. There may have been a few instances of latent diabetes among this second group. However, at least 60 per cent of these patients had blood sugar determinations while they were under observation.

A summary of the analysis of this study is shown in table 1. It will be noted that:

1. The *absolute incidence of arteriosclerosis* to a degree of causing arterial insufficiency is very significantly higher in the so-called diabetic group in every decade when diabetic patients are compared to nondiabetic patients as a group. The ratio for the entire group, meaning both diabetic and nondiabetic patients, is approximately 11:1.

2. Arteriosclerosis obliterans occurs a decade later among nondiabetic patients as a group than it does among diabetic patients.

3. The same general remarks apply when the conditions of diabetic and nondiabetic males are compared.

4. Arteriosclerosis obliterans occurs two decades later among nondiabetic women than it does among diabetic men, and it occurs one decade later among nondiabetic women than it does among diabetic women.

5. The incidence of arteriosclerosis obliterans among diabetic women is almost 80 times as frequent as it is among nondiabetic women as a group.

6. Even in the age period of as early as 40 to 49 years, arteriosclerosis obliterans is about 12 times as common among diabetic women as it is among nondiabetic men.

7. The ratio of men to women in the nondiabetic group is approximately 7:1.

TABLE I
Arterial Occlusive Disease among Diabetic and Control Patients

Age, Years	Total Male and Female Patients					Male Patients					Female Patients				
	Diabetes*			Control†		Diabetes			Control		Diabetes			Control	
	Total	Arterial Occlusive Disease		Total	Per 1000	Total	Arterial Occlusive Disease		Total	Per 1000	Total	Arterial Occlusive Disease		Total	Per 1000
		Num-ber	Per 1000				Num-ber	Per 1000				Num-ber	Per 1000		
30-39	615	4	6.5	52,802	0	342	4	11.7	23,049	0	273	0	0	29,753	0
40-49	1,370	12	8.8	58,106	10	758	9	11.9	28,055	10	612	3	4.9	30,051	0
50-59	2,359	82	34.8	47,554	51	1,251	53	42.4	24,231	48	1,108	29	26.2	23,323	0.1
60-69	2,071	93	44.9	28,563	96	1,156	67	58.0	16,100	83	915	26	28.4	12,463	1.0
70-79	604	33	54.6	9,671	49	376	20	53.2	6,084	41	228	13	57.0	3,587	2.2
80+	54	6	111.1	1,198	13	41	4	97.6	781	11	13	2	153.8	417	4.8
Total	7,073	230	32.5	197,894	219	3,924	157	40.0	98,300	193	3,149	73	23.2	99,594	0.3

* Diabetes series consists of cases, 1928-1938, inclusive.

† Control series consists of all non-diabetic cases, 1929-1933, inclusive.

8. The ratio of men to women in the diabetic group is approximately 2:1. This is otherwise expressed (table 1):

Fifty-six per cent (41 of 73) of diabetic women having occlusive peripheral arteriosclerosis were 60 years or more.

Fifty-eight per cent (91 of 157) of diabetic men having occlusive peripheral arteriosclerosis were 60 years or more.

Seventy per cent (135 of 193) of nondiabetic men having occlusive peripheral arteriosclerosis were 60 years or more.

Eighty-eight and four-tenths per cent (23 of 26) of nondiabetic women having occlusive peripheral arteriosclerosis were 60 years or more.

It is equally enlightening to note the incidence of the more serious complications of occlusive peripheral arteriosclerosis as represented by gangrene or trophic ulcers.

Among the nondiabetic group as a whole, 107 patients (48.9 per cent) of 219 patients having occlusive peripheral arterial disease had gangrene or trophic ulcers.

Among the diabetic group as a whole, 143 patients (62.1 per cent) of 230 patients had gangrene or trophic ulcers.

Among 193 nondiabetic men having occlusive peripheral arterial disease, 95 (49.4 per cent) had gangrene or trophic ulcers.

Among 157 diabetic men having occlusive peripheral arterial disease, 85 (54.1 per cent) had gangrene or trophic ulcers.

Among 26 nondiabetic women having occlusive peripheral arterial disease, 12 (46.1 per cent) had gangrene or trophic ulcers.

Among 73 diabetic women having occlusive peripheral arterial disease, 58 (79.4 per cent) had gangrene or trophic ulcers.

In summary then, this study shows a markedly higher absolute incidence for occlusive peripheral arteriosclerosis among diabetic patients, as well as a significantly higher incidence of the more severe complications of arteriosclerosis. Most striking of all is the enormously increased vulnerability, not only to occlusive peripheral arteriosclerosis, per se, but also to the more serious complications of arteriosclerosis, of women who have diabetes. This is especially significant when the usual increased vulnerability of the male to most chronic diseases is considered.

COMMENT

The question of how closely a direct cause and effect relationship can be established between diabetes and arteriosclerosis is a matter for conjecture. The mere association of the two conditions in a patient is probably only one facet of a many-sided crystal. The question of the parts that the disturbed carbohydrate metabolism and the deranged fat metabolism during phases of ketosis play comes to the fore, but it must be noted that in the condition of a patient who has both diseases, there is no direct relationship between the

severity of diabetes and the degree of arteriosclerosis present. The most marked forms of arteriosclerosis are often encountered in the presence of mild diabetes. Indeed, there are instances in which the obliterative disease antedates the known onset of diabetes. The state of altered metabolism then, is merely another facet of the same crystal.

Perhaps it would be more nearly correct to regard the problem in the light of an abiotrophy affecting both the insulin-producing tissues and the vascular systems alike, and to suggest that a condition is present which requires merely an additional stimulus to bring about arterial lesions of pathologic proportions, just as it requires an additional stimulus, such as obesity, over-feeding, or an infectious illness, for diabetes to become manifest. This additional stimulus may be hypertension in one instance, hyperlipemia as we encounter it in hypothyroidism or xanthomatosis in another instance. Again, the added metabolic strain caused by obesity may be sufficient to initiate or at least hasten the progress of arteriosclerosis. Diabetes, as well as arteriosclerosis, exhibits strong hereditary trends. We postulate, in short, a biologic background for arteriosclerosis. To illustrate, let us call to mind the vulnerability of the arterial system of the rabbit to the feeding of cholesterol,² as compared to the relative immunity of the arterial systems of other animals to this substance.

CERTAIN PHENOMENA CHARACTERISTIC OF DIABETES WHICH BEAR A DIRECT OR INDIRECT RELATIONSHIP TO THE PROBLEM OF DEGENERATIVE ARTERIAL DISEASE IN GENERAL

The study of certain associated phenomena characteristic of diabetes was also carried out in order to determine whether or not such phenomena would cast some light on the genesis of arterial disease among those individuals whose biologic or metabolic backgrounds seemed to have rendered them more susceptible to more rapidly progressive arterial disease.

Previous surveys of diabetic patients have disclosed a striking relationship between arterial disease, diabetic retinitis and so-called diabetic neuritis. In 1934, Wagener, Wilder, and one of us (Dry³) found that 25 per cent of 187 diabetic patients suffering from hemorrhagic lesions of the retina showed evidence of having some abnormality of the peripheral nerves as compared to only 8 per cent of a control series of 371 patients having diabetes consecutively encountered (not exhibiting retinal lesions of the diabetic type). The clinical records revealed significant disease of the arteries or kidneys in 84.5 per cent of the 187 patients having hemorrhagic lesions of the retina, and in only 53.3 per cent of 371 patients who had no retinal lesions of the diabetic type. In fact, there were only 23 patients in the entire series³ in which diabetic retinal disease was not associated with clinically demonstrable arterial disease, an observation which does not, of course, mean that such arterial disease was not present.

A study of the evolution of retinal disease in the presence of diabetes led to the belief that diabetes injures the finer arterioles or venules of the retina (probably the venules), and that the injury is insufficient in degree in most instances to bring about abnormalities that are visible with the ophthalmoscope. In more marked degree, however, this injury to the arterioles or venules gives rise to characteristic punctate hemorrhages; later these hemorrhages are associated with the appearance of punctate exudates or cotton wool-like structures or both. Finally, lesions of the veins occur, resulting in recurrent hemorrhages into the vitreous, producing the picture of retinitis proliferans.

The point requiring emphasis is the fact that disease of the finest radicles of the arterial and venous system initiates changes, which in turn set the stage for progressive degenerative lesions of the retina. At least, as far as the retina is concerned, the diabetic process seems to be principally responsible for these changes, since they occur in the presence of no other disease.

TABLE II
Relative Incidence of Gangrene, Retinitis and Neuritis among Diabetic Males and Females, Respectively

Gangrene	85 of 157 males, or 54.1 per cent 58 of 73 females, or 79.4 per cent
Neuritis	31 of 157 males, or 20 per cent 22 of 73 females, or 30.1 per cent
Retinitis	48 of 131 males, or 36.6 per cent 48 of 65 females, or 74 per cent

In the present study (table 2), the retinas of 196 patients of the diabetic group (131 men and 65 women) were examined. Evidence of the existence of one or another type of diabetic retinitis was observed of 96 patients, or 49 per cent of the 196 diabetic patients having occlusive peripheral arteriosclerosis, as compared to the incidence for retinitis of 17.7 per cent among the general type of diabetic patients encountered.³

In consonance with the high incidence of the more advanced forms of arteriosclerosis obliterans noted among female diabetic patients, it is interesting to note that of the 65 diabetic women of the present series having occlusive peripheral arterial disease, for whom retinoscopy was done, no less than 48 had a diabetic type of retinitis—that is, approximately 74 per cent (table 2). In marked contrast to this figure, the eye grounds of only 48 of the 131 diabetic male patients of the present series exhibited a diabetic type of retinitis—that is, 36.6 per cent.

How then is the interrelationship completed between arteriosclerosis and so-called diabetic neuritis on the one hand, and diabetic retinitis on the other? In considering diabetic neuritis by itself for a moment, there are several features requiring comment.

First, there seems to be no direct relationship between the metabolic disturbances associated with diabetes per se and involvement of the peripheral nerves, since the incidence of peripheral neuritis is no higher among patients with severe diabetes than among those with milder forms of the disease. Indeed, the reverse is actually more often true. Peripheral neuritis among young individuals who invariably suffer from the most severe grades of diabetes, occurs but rarely and when it does, its clinical behavior is strikingly different from that of the more common type of so-called diabetic neuritis of older patients. Thus, involvement of the peripheral nerve among juvenile diabetic patients clears up as the diabetes is controlled, suggesting that the basis for its existence might very well be avitaminosis conditioned by the associated nutritional derangement; the involvement of peripheral nerves among older diabetic patients is notoriously refractory to treatment even when the diabetes is adequately controlled. Because of this difference in its clinical behavior and because of its rarity, the peripheral neuritis of young diabetic patients will not be considered in the discussion which follows.

The second, and by far the most important consideration, arises out of histologic studies of nerve trunks obtained from patients who had exhibited evidence of having peripheral neuritis. Woltman and Wilder,⁴ in a study of 10 such cases, made the following observations: (1) degenerative changes were present in all instances, and were either patchy or diffuse, and the severity of symptoms and the degree of degeneration did not show any correlation, (2) in practically every instance, there was marked thickening of the walls of the intraneural nutrient arterioles, and (3) marked peripheral arteriosclerosis was associated with every case studied.

In short, diabetic neuritis is essentially an ischemic neuritis and its genesis is dependent on interference with the vascular supply to the nerve bundles. In this respect it resembles in every way the ischemic neuritis associated with peripheral arteriosclerosis afflicting a nondiabetic patient.

Thus far, present methods of examination have not identified a histologic lesion associated with diabetic neuritis which can be regarded as specific for diabetes, as are the punctate hemorrhagic lesions in the deeper layers of the retina. On the other hand, hemorrhagic extravasations within the walls of arteries have been shown by Winternitz, Thomas and LeCompte⁵ to be a very common finding when specimens are studied after proper clearing. Again, the relationship of these extravasations to the vasa vasorum becomes important since these authors have shown repeatedly that "at the juncture of a branch with the parent vessel, one finds not only the greatest number of vasa vasorum, but also the majority of hemorrhages, and, likewise atheromata." The inference again is that involvement of the nutrient arteries is the basis for certain degenerative changes and that the hemorrhagic extravasation and necrosis incidental to such degenerative changes furnish a nidus for future deposition of calcium and the atheromatous plaque.

The analysis of our cases reveals again a greater vulnerability on the part of the female diabetic patients who have arteriosclerosis obliterans to involve-

ment of peripheral nerves than would be the case concerning male diabetic patients who have arteriosclerosis obliterans. Thus, 22 or 30.1 per cent of 73 diabetic women having occlusive peripheral arteriosclerosis (79.4 per cent of these 73 women had gangrene) presented evidence of involvement of the peripheral nerves as compared to 31 or 20 per cent of the 157 male diabetic patients suffering from occlusive peripheral arteriosclerosis (54.1 per cent of these 157 men had gangrene).

As a group, 23 per cent of diabetic patients suffering from occlusive peripheral arteriosclerosis had neuritis. Table 2 indicates the relative frequency of occurrence of the triad—gangrene, diabetic retinitis and peripheral neuritis—among male and female diabetic patients respectively.

TABLE III
The Distribution of Gangrene, Retinitis and Neuritis among Diabetic Patients
Having Occlusive Peripheral-Arterial Disease

Male Patients				
Age	Number	Gangrene	Retinitis	Neuritis
30-39	4	2	3	1
40-49	9	7	5	2
50-59	53	25	7	9
60-69	67	33	25	17
70-79	20	16	7	2
80-89	4	2	0	0
Totals	157	85	47	31
Female Patients				
30-39	0	0	0	0
40-49	3	2	1	1
50-59	29	25	25	9
60-69	26	20	13	8
70-79	13	9	9	4
80-89	2	2	0	0
Totals	73	59	48	22

Further, it is to be noted in table 3 that the decades during which occurred the highest incidence of retinitis were also the ones in which the incidence of neuritic involvement was the highest. Indeed, this is as true in the age period of 50 to 59 years among the female patients as it is in the next decade of 60 to 69 years, whereas the male patients show the highest preponderance of the components of the triad only in the age period of 60 to 69 years.

The inference that a common factor is responsible for the initiation of arteriosclerosis in the presence of diabetes on the one hand and for the initiation of diabetic retinitis and diabetic neuritis on the other (on the basis of the frequent correlation of these lesions) deserves serious consideration. This common factor is interference with nutrient vessels concerned in each instance: in retinitis, the retinal arterioles; in neuritis, the vasa nervorum; in intimal arteriosclerosis, the vasa vasorum.

SUMMARY AND CONCLUSIONS

1. The incidence of arteriosclerosis obliterans is far greater among diabetic individuals than among those who do not have diabetes mellitus.

2. The female diabetic patient exhibits an unusual vulnerability to arteriosclerosis.

3. Diabetic retinitis and diabetic peripheral neuritis occur with great frequency among diabetic patients who are also afflicted by arteriosclerosis obliterans; the incidence of both retinitis and neuritis is significantly higher among female diabetic patients who also have arteriosclerosis obliterans than it is among male diabetic patients afflicted with arteriosclerosis obliterans.

4. We postulate that a biologic background exists for the development of advanced arteriosclerosis in the presence of diabetes mellitus. By this we imply that an inherent weakness or abiotrophy exists which affects both the insulin-producing tissues and the vascular system, which requires in each instance only an additional stimulus to bring about pathologic changes in the structure of the insulin-producing tissues and the vascular system. In the case of the former, an infectious illness, overfeeding, or obesity, and in the case of the latter, hypertension, obesity or hyperlipemia, may serve as adequate stimuli for the initiation of the lesion, at least, the progression of the lesion, once it has been initiated. This phenomenon is analogous to the variability in the vulnerability of different animals to arteriosclerosis under experimental conditions, as for example, during the feeding of cholesterol.

5. On the basis of the frequent association of arteriosclerosis obliterans, retinitis, and peripheral neuritis among diabetic patients and on the basis of certain anatomic observations made in the presence of retinitis and neuritis, we postulate that a common mechanism exists for the production of these three entities; namely, involvement of the nutrient vessels concerned in each instance; in retinitis, the retinal arterioles; in neuritis, the vasa nervorum; in intimal arteriosclerosis, the vasa vasorum.

REFERENCES

1. ROOT, H. F., BLAND, E. F., GORDON, W. H., and WHITE, P. D.: Coronary atherosclerosis in diabetes mellitus; a postmortem study, *Jr. Am. Med. Assoc.*, 1939, cxiii, 27-30.
2. ANITSCHKOW, N., and CHALATOW, S.: Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, *Centralbl. f. allg. Path. u. path. Anat.*, 1913, xxiv, 1-9.
3. WAGENER, H. P., DRY, T. J., and WILDER, R. M.: Retinitis in diabetes, *New England Jr. Med.*, 1934, ccxi, 1131-1137.
4. WOLTMAN, H. W., and WILDER, R. M.: Diabetes mellitus; pathologic changes in the spinal cord and peripheral nerves, *Arch. Int. Med.*, 1929, xlv, 576-603.
5. WINTERNITZ, M. C., THOMAS, R. M., and Lecompte, P. M.: The biology of arteriosclerosis, 1938, Charles C. Thomas, Springfield, Illinois, pp. 80-93.

CASE REPORTS

AN ATYPICAL HEMOLYSIN IN PREGNANCY*

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THE case to be reported is one of 12 (of which five were selected from the literature) recently cited in support of the hypothesis that the pregnant woman under certain conditions may be immunized by the products of conception; i.e., fetus or placenta.¹ This hypothesis was offered by Levine and Stetson² as an explanation for the origin of an atypical agglutinin with the properties of an immune antibody, observed in a pregnant woman never previously transfused. It was assumed that the patient, who had harbored a dead fetus for two months, was immunized by an agglutinin in the blood or tissues of the macerated fetus, inherited from the father. A review of the obstetrical history and the present pregnancy in the 12 cases revealed, in almost all of them, the presence of a number of complications, such as toxic symptoms, repeated abortions, macerated fetuses, and post-partum infections.

The patient under consideration presents the following features of interest: a past history of 11 pregnancies, including four miscarriages; toxic symptoms during the eleventh pregnancy; in the present pregnancy (twelfth) mild toxic symptoms, endometritis during the puerperium, and transfusion shock due to an atypical isoantibody, in this case a hemolysin.

Reports of atypical isohemolysins in the literature are very few, and a brief description of these cases is given below.

In 1932 Parr and Krischner³ described a fatal transfusion accident in a woman (group O) suffering from loss of blood following an incomplete abortion. Administration of her husband's blood, which was in group O and believed to be compatible, resulted in an immediate acute transfusion shock which terminated fatally four and one-half hours later. Subsequent examination revealed that although donor and patient were in group O, nevertheless, the donor's cells mixed with patient's serum underwent slow hemolysis which masked the agglutination.

In the second case reported by Neter⁴ the patient, suffering from subacute bacterial endocarditis, was transfused uneventfully three times in February 1935. Six weeks later it was observed that his serum contained an atypical agglutinin and hemolysin which acted on about 25 per cent of all bloods. This antibody could no longer be demonstrated the following month.

Very brief reference is made by DeGowin⁵ to two patients in whom atypical hemolysins, active on the donor's cells, were found. These observations were made after the onset of transfusion shock which proved to be fatal. In one case the patient had numerous transfusions because of bleeding from the colon;

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the other, a patient with nephritis, had an uneventful transfusion four days previously.

Reports of post-transfusion hemolytic reactions in instances where the bloods were presumably compatible are numerous, but two recent cases occurring in post-partum patients were published by Mandelbaum⁶ and Brainard.⁷

A brief résumé of the significant points in the history of the present case follows:

Patient M. St., aged 37, was admitted in labor to one of the hospitals in New York City. She gave a history of 11 previous pregnancies and of these seven were full-term and four resulted in miscarriages. The previous labors were uneventful, except for the appearance of hypertension with the eleventh pregnancy.

During the entire period of the present pregnancy the patient complained of occasional vomiting, moderate dependent edema, some spots before the eyes, and nocturia.

TABLE I
Tests at 20° C. with Unheated Serum M. St.

Read after	Red Blood Cells of Group O				
		1	2	3	4
1½ hours at 20° C.	agg. hem.	+± 0	+± 0	0 0	0 0
1½ hours at 37° C.	agg. hem.	tr s	± s	0 0	0 0
Immediate centrifuging and resuspension	agg. hem.	+± 0	+± 0	0 0	0 0

Tests were made by mixing two drops of serum and two drops of 2 per cent washed cell suspensions.

Agg. = agglutination; hem. = hemolysis; the signs +±, +, ±, and tr (trace) indicate varying intensities of agglutination; s = strong.

A normal, living, full-term infant was delivered on November 19, 1939, after five hours of labor. Two days later, the patient's temperature rose to 101°, abdominal tenderness could be elicited at the umbilical region and the following day foul lochia appeared. On November 23 the patient was put on intensive sulfanilamide therapy for a period of three days. The temperature was still high on November 30, at which time the hemoglobin determination was 56 per cent (Dare).

On the twelfth day post partum, the patient (group A) received a transfusion of group A blood. Despite the advisedly slow and careful injection of the blood, for reasons mentioned below, the transfusion had to be discontinued because of the onset of a chill after 150 c.c. of blood were introduced. The pulse rate increased to 124 and respiration to 24 per minute. The patient vomited once and the temperature rose to 105.2° within two hours, but soon returned to normal. The following morning, a catheterized specimen of urine showed in addition to albumin and casts the presence of blood as indicated by a positive benzidine test and some red blood cells observed microscopically. (A catheterized specimen drawn the day before the transfusion was entirely normal.) A specimen drawn the day after the transfusion showed diminished albumin and casts and no blood. The hemoglobin at this time was 48 per

cent (Dare). The patient was given large doses of alkali and general supportive treatment. She was discharged 24 days after admission with the diagnosis of "parturition and acute puerperal endometritis."

In the pre-transfusion compatibility tests for the selection of the donor, it was observed that the patient's serum did agglutinate the donor's cells at room temperature, but since these reactions apparently disappeared or were not observed at 37° C., it was considered safe to transfuse the patient with this particular blood. In other words it was felt that the agglutinin in question was a cold agglutinin.

Subsequently, tests done at both 20° C. and 37° C. with the patient's pre-transfusion specimen confirmed the presence of distinct agglutination at the lower temperature; but in the corresponding tests kept at 37°, the agglutination was masked and obliterated by distinct but incomplete hemolysis (table 1).

TABLE II
Hemolysis, Inactivation, and Reactivation

		Red Blood Cells of Groups					
		O	O	A	A	O	A
		FC	CM	PB	FP	WE	PL
I Unheated serum M. St. 1 hour at 37° C.	agg.	±	±	±	tr	0	0
	hem.	vs	vs	vs	s	0	0
II Inactivated serum M. St. 1 hour at 37° C.	agg.	+ ±	+ ±	+ ±	+	0	0
	hem.	0	0	0	0	0	0
III Addition of fresh normal serum P.B. to tubes in II 1 more hour at 37° C.	agg.	++	++	++	+ ±	0	0
	hem.	s	d	d	d	0	0

agg. = agglutination; hem. = hemolysis; vs = very strong; s = strong; d = distinct.

When numerous bloods of groups O and A were tested at 37° C. with fresh and inactivated sera, parallel hemolytic and agglutination reactions were observed (table 2, I and II). In other words, distinct but incomplete hemolytic reactions were observed in tests with unheated serum, and the same bloods were selected by agglutination in the tests with inactivated serum. Of 67 bloods of group O, 18 bloods (27 per cent), and of 48 group A bloods 12 (25 per cent) were found to be sensitive.

As is indicated in table 1, the results were clear cut if the procedure recommended for the direct compatibility test was employed; i.e., centrifuging the test mixtures at low speed without any incubation, and readings made after resuspending the sedimented cells.

The hemolytic reactions with the inactivated serum could be restored by incubating the test mixture with fresh normal group A serum (table 2, II and III).

The weak degree of hemolysis and the more intense agglutination in the reactivated series in contrast to the results with fresh serum (compare III and I in table 2) may be attributable to the conditions of the experiment; i.e., the addition of normal fresh (complement bearing) serum to cells already specifically agglutinated and consequently more resistant to hemolysis than free cells:

Titration of this serum (group A) with two bloods (Groups O and A) sensitive to the atypical antibody showed an end-point of 1:16 in contrast to a value of 1:256 for the activity of the normal anti-B agglutinin. These results were obtained in tests that were kept for two hours at 37° C. It is to be noted that the atypical antibody in this serum was far more potent than in the blood described by Neter.⁴

The comparatively high value of the anti-B agglutinin in the group A mother is of interest since the infant of the last pregnancy belonged to group B. As has been shown by Jonsson,⁸ a high anti-B titer is to be expected under such conditions. On the basis of his experiments Jonsson concludes that the fetus in so-called heterospecific pregnancies frequently immunizes the mother.

The serum was tested at various intervals after the transfusion accident and, at the last examination, 16 months post-partum, the agglutinin and the hemolysin could still be demonstrated, although there was distinct diminution of activity. The persistence in the activity of the antibody need not constitute proof that it is not an immune body. In support of this is the observation of Levine and Landsteiner⁹ on the persistence of an immune isoagglutinin in one rabbit for over a period of seven months until the animal died. In the case previously reported with Stetson, the isoagglutinin could no longer be demonstrated at the end of a year. Further observations as to the persistence of the atypical antibody in the case of M. St. will be made.

The specificity of the antibody in serum M. St. was such that it selected bloods independently of the factors M, N, or P. On the basis of more recent tests, it can be stated that this hemolysin shows a different specificity from that exhibited by the anti-Rh of Landsteiner and Wiener.^{10, 11} This becomes evident also from a comparison of the incidences of positive and negative reacting bloods (25 per cent positive with serum M. St. and 85 per cent with anti-Rh). It may be mentioned that a similar frequency of positive agglutination (25 per cent) was noted in the atypical antibody described by Neter.⁴

More definite information on the specificity would be available, if a corresponding immune heteroagglutinin could be prepared. With this in view, four rabbits and four guinea pigs were given a series of injections with sensitive blood (group O, type M), but an antibody corresponding to that in the serum M. St. could not be obtained.*

DISCUSSION

This case is of interest because of the presence in a post-partum patient of an atypical isoantibody with hemolytic action which was responsible for a moderate post-transfusion shock. As to the origin of the antibody, it is assumed that in the absence of a history of previous blood transfusions, the mother was immunized either in the course of previous pregnancies or in the course of the

* Of the four rabbits, three produced potent anti-M agglutinins, while the fourth rabbit yielded a moderately active serum.

present pregnancy or puerperium.* The persistence of the antibody for at least 16 months would seem to indicate an intensive immunization which, a priori, is plausible in view of the multiple pregnancies of which four were miscarriages. The relationship, if any, of the hypertension throughout the seventh pregnancy and the mild toxic symptoms throughout the present pregnancy to the supposed isoimmunization, cannot be established, at least for the present.

In a general way, it may be stated that one reason for the difficulty in detecting this type of incompatibility lies in the fact that atypical antibodies are considerably weaker in activity than the anti-A or anti-B isoantibodies.¹² Nevertheless, rapid and sensitive methods are available to detect even such incompatibilities; e.g., centrifuging and resuspension of the sedimented cells.

More specifically, the difficulty in this case and in the case of Parr and Krischner³ was the failure to detect, in the compatibility test, the slow action of the hemolysin, which masked the agglutination. This was stated concisely by Parr and Krischner who write as follows: "The hemolysin was not so rapid as to call attention to its occurrence in the usual cross-matching and in the complete absence of any agglutination in these preparations, it was assumed that the bloods were completely compatible." In both cases tests were performed by incubating the mixture of patient's serum and donor's cells at 37° C. The confusing effects of this hemolysis, however, could be avoided by resorting to the centrifuging technic without previous incubation, or by performing the tests with inactivated patient's serum. In any event, it is important to bear this in mind, and it is suggested that a further precaution be taken; i.e., to start the transfusion slowly so that it can be interrupted before too large a volume is injected, as was done in the present case. This measure, the so-called biologic test, was recommended a number of years ago by Oehlecker.¹³

An answer to the question why atypical antibodies induce hemolysis only in some instances cannot be given at present. In a general way it may be stated that the individuality of the person immunized and the chemical nature of the antigenic components of the blood or tissue cells are two determining factors. In this connection it is of interest to recall the significant observation of Landsteiner and van der Scheer dealing with the hemolysin: agglutinin ratio of the two sorts of immune sera produced by immunization with red blood cells on the one hand, and with alcoholic extracts of red blood cells mixed with antigenic protein on the other.¹⁴ A considerably greater content of hemolysin was found in the extract-immune sera. These observations suggest a similar special sort of immunization for the cases under discussion. In any event, *in vivo* hemolysis of transfused sensitive blood can occur in the presence or absence of *in vitro* hemolysis.

Our knowledge of atypical antibodies in pregnancy is indeed fragmentary because the source of material investigated until now was derived almost exclusively from women who received incompatible blood. In many patients, more

* The rôle of isoimmunization of the mother by blood properties in the fetus inherited from the father in the pathogenesis of erythroblastosis fetalis (fetal hydrops, icterus gravis and congenital anemia of the new born) has recently been discussed by Levine, Katzin and Burnham (Jr. Am. Med. Assoc., 1941, cxvi, 825). The blood factor Rh is involved in the great majority of cases (69) but in the six exceptions, i.e., in which the mother's blood contained the Rh factor, it can be assumed that another blood factor is involved. Tests of these six cases indicate that possibly the blood factor detected by the hemolytic antibody described in this paper may also immunize the mother and thus induce erythroblastosis fetalis. These findings represent unpublished work by Levine and his collaborators, Vogel, Katzin, Burnham and Goldman.

fortunate in either not requiring blood transfusion or in receiving compatible blood, the atypical antibody is never recognized, or if so, not studied.

A systematic investigation of a large number of blood specimens from cases of pregnancy, normal and pathologic, is highly desirable and such a study should yield data as to the correctness of the conception of isoimmunization of the mother by the fetus. Further support of the hypothesis can be derived from testing in each instance the action of the atypical agglutinin on the cells of the husband, provided he is compatible according to the blood groups.

SUMMARY

A case is reported of an intra-group hemolysin which was observed during the puerperium of a patient never previously transfused. The origin of the antibody is assumed to be in the immunization of the mother by the fetus or the fetal parts of the placenta.

Attention is called to the hemolysin as a source of error in the direct compatibility test since weak or moderate hemolysis masks agglutination. The reactions of this atypical antibody could be readily detected if the centrifuging technic is employed for the direct compatibility test.

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BIBLIOGRAPHY

1. LEVINE, PHILIP, and KATZIN, E. M.: Isoimmunization in pregnancy and the varieties of isoagglutinins observed, *Proc. Soc. Exper. Biol. and Med.*, 1940, xlv, 343-346.
2. LEVINE, PHILIP, and STETSON, R. E.: An unusual case of intra-group agglutination, *Jr. Am. Med. Assoc.*, 1939, cxiii, 126-127.
3. PARR, L. W., and KRISCHNER, H.: Hemolytic transfusion fatality with donor and recipient in the same blood group, *Jr. Am. Med. Assoc.*, 1932, xcvi, 47.
4. NETER, E.: Observations on abnormal isoantibodies following transfusions, *Jr. Immunol.*, 1936, xxx, 255-259.
5. DEGOWIN, E. L.: Grave sequelae of blood transfusions: a clinical study of 13 cases occurring in 3500 blood transfusions, *ANN. INT. MED.*, 1938, xi, 1777-1791.
6. MANDELBAUM, H.: Hemolytic reaction following blood transfusion: report of a case of intra-group incompatibility, *ANN. INT. MED.*, 1939, xii, 1699-1708.
7. BRAINARD, H. H.: Renal insufficiency following transfusion of compatible blood, *Am. Jr. Obst. and Gynec.*, 1940, xl, 142-144.
8. JONSSON, B.: Zur Frage der heterospezifischen Schwangerschaft, *Acta Path. e. Micr. Scand.*, 1936, xiii, 424-433.
9. LEVINE, PHILIP, and LANDSTEINER, K.: On immune isoagglutinins in rabbits, *Jr. Immunol.*, 1929, xvii, 559-565.
10. LANDSTEINER, K., and WIENER, A. S.: An agglutinable factor in human blood recognized by immune sera for Rhesus blood, *Proc. Soc. Exper. Biol. and Med.*, 1940, xliii, 223.
11. WIENER, A. S., and PETERS, H. R.: Hemolytic reactions following the transfusion of blood of the homologous group with three cases in which the same agglutino-gen was responsible, *ANN. INT. MED.*, 1940, xiii, 2306-2322.
12. LANDSTEINER, K., and LEVINE, PHILIP: On isoagglutinin reactions of human blood other than those defining the blood groups, *Jr. Immunol.*, 1929, xvii, 1-28.
13. OEHLECKER, F.: Erfahrungen aus 170 direkten Bluttransfusionen von Vene zu Vene, *Arch. f. klin. Chir.*, 1921, cvi, 705-719.
14. LANDSTEINER, K., and VAN DER SCHEER, J.: On the antigens of red blood corpuscles, *Jr. Exper. Med.*, 1925, xli, 427-437.

DIAPHRAGMATIC TIC; A CASE REPORT*

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A variety of respiratory disorders are known to develop as a consequence of epidemic encephalitis and most of the reported cases of diaphragmatic tic have been of this character. Other cases have less frequently presented no apparent relation to any acute infectious process but are allied with gastrointestinal and circulatory malfunction. The case reported here is of that group.

A white American female, aged 36 years, was first seen by me on February 15, 1938. Her chief complaint at that time was of a distressing train of events following the ingestion of food which she described as follows:

"Sometimes at the beginning of a meal, more often during the course of the meal, and most often following its conclusion, I am attacked with a severe upper abdominal pain. Coincident with the beginning of pain a most distressing vibration of the entire upper half of my body sets in. Over this vibration I have no control. It is extremely painful and sometimes I feel the pain beneath my left shoulder blade. I am unable to move except with the greatest difficulty. Occasionally vomiting accompanies the attack but I would say that is rather rare. Above the dull thumping produced by the tumult of my body I can at times hear a distinct splashing sound in the upper abdomen."

At the time the patient was first examined she was resting comfortably in bed, and a complete history leading to the present condition was elicited at that time.

The patient had been perfectly well up to June 6, 1933 when she developed attacks of vomiting, distress in the epigastrium and continuous pain in the lower abdomen which tended to become localized in the right lower quadrant. There had been a loss of weight, dyspnea, dysuria and moderate vesical tenesmus. She was admitted to St. Vincent's Hospital, Bridgeport, Conn., for observation and treatment.

With a pre-operative diagnosis of pyloric stenosis and partial intestinal obstruction, the patient was operated upon. A Mayo type pyloroplasty was done. Following this the patient showed considerable improvement for about three months.

In September 1933 she was re-operated upon for intestinal obstruction due to a kinking of the duodenum noted only when she was in an upright position. At this time a posterior gastroenterostomy was done. A very definite atony of the whole gastrointestinal tract was noted. Recovery was impeded by the development of a left parotitis.

Another period of relief was accompanied by a gain in weight. Several months later the patient began to regurgitate food and to complain of colicky pain in the lower abdomen. Regurgitation became more frequent and pain more severe. There was a progressive loss of weight and a rapidly developing asthenia.

In April 1934, another laparotomy was done and a portion of the transverse colon was found adherent to the left side of the pelvis. The stomata of the pylorus and of the gastroenterostomy were both patent. There was no gastric retention. The adhesions were freed; the greater omentum was brought anterior to the bowel and secured to the anterior abdominal wall to prevent recurrence of adhesion between gut and wall. Recovery was uneventful and the patient progressively improved.

She continued to be fairly comfortable until January 1937. At this time there was a recurrence of regurgitation, accompanied by abdominal pain, nausea and distention. She was somewhat relieved at this time by antispasmodics but complete

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obstipation shortly intervened. A diagnosis of intestinal obstruction due to the presence of adhesive bands was made and operation again advised. At operation extensive adhesions were found blocking the third portion of the duodenum. An enterostomy was done after all adhesions had been liberated and the raw surfaces reperitonealized. The abdomen was closed without drainage.

Again the patient made a good recovery and the progress of normal health was not interrupted until February 1938. At this time the chief complaint already referred to made itself evident.

On examination, a fairly well developed, well nourished young woman was seen lying comfortably in bed. Examination of the eye-grounds, extraocular movements, ears, nose and throat was negative. The lungs were negative. The heart was normal in size and in position. No murmurs or friction rubs were heard. No arrhythmias were noted. The blood pressure was systolic 110, diastolic 70. The respiratory rate was 20. The abdomen was soft and flaccid and many scars of previous operations were noted. Examination of the pelvis, rectum and extremities was negative. Routine neurologic examination and examination of blood and urine specimens showed no abnormalities.

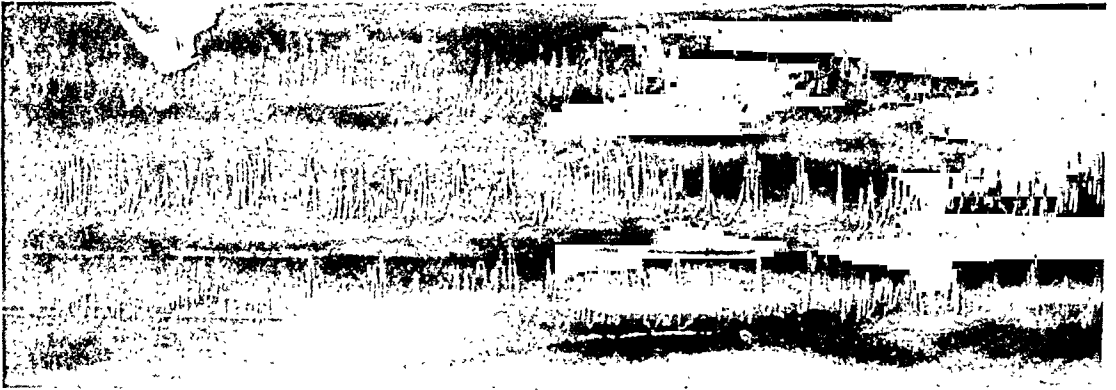


FIG. 1. Greatly reduced photograph of a plethysmographic record showing 128 contractions of diaphragm in 60 seconds.

The patient was given a sandwich and a glass of milk and was asked to eat and drink as she would when taking lunch. She did this slowly and with apparent relish. A few moments afterward the entire physical picture was dramatically changed. At a rapid but irregular rate the upper half of the patient's body began to vibrate vigorously. Respirations came in grunts and gasps, too rapidly to be counted. Her upper abdominal wall rose and fell in irregular rhythm and with unusual force and amplitude. Her face was suffused and slightly moistened with perspiration and contorted with pain. Standing at the bedside, an easily audible succussion sound could be heard and it appeared to be synchronous with the visible vibration of her body. The patient was placed in an upright position behind a fluoroscopic screen. She was able to drink a glass of barium mixture with some difficulty. The barium was seen to enter the stomach freely. The stomach could be visualized in a rapid shuttle-like type of activity, being buffeted downward by the downward excursion of the diaphragm. The barium was seen to pass without obstruction both into the duodenum and through the gastroenterostomy stoma. The diaphragm was noted to be in constant clonic contractions, the upward and downward excursions being easily seen and covering an estimated amplitude of about six inches. As the diaphragm rose jerkily upward it elevated the heart high in the mediastinum and displaced it slightly to the right. Heart sounds could be heard with the stethoscope during the tumult. The

pressure of the diaphragm against the heart seemed to slow its rate. The composite clinical picture was (1) extreme upper abdominal and lower thoracic agitation, (2) pain, (3) hyperventilation of lungs, (4) alkalosis and (5) mild tetany. The attack lasted for about one hour and was controlled by hypodermic injection of dilaudid gr. 1/32. During the subsequent attacks, attempts at relief with various drugs, carbon dioxide inhalations, tongue traction, short wave diathermy and deep roentgen-ray therapy were of no avail.

On the following day during a repetition of the attack an electrocardiogram was made and showed changes indicative of myocardial damage. Another electrocardiogram taken while the patient was free from any disturbance, produced the same changes noted in the first tracing; i.e. slurring and notching of the R-wave in Lead I and diphasic T-wave in Lead III.

Plethysmographic tracings made with the belt around the body at various levels between the umbilicus and the breasts, showed the average rate of the diaphragmatic contractions to be 128 per minute.

Blood calcium readings ranged between 9.2 and 10.4 mg. per 100 c.c. of serum.

Carbon dioxide combining power determinations made during the attack, when hyperventilation was at its height, were found to be:

Feb. 20	38 vol. per cent,
Feb. 25	35 vol. per cent,
Mar. 8	35 vol. per cent.

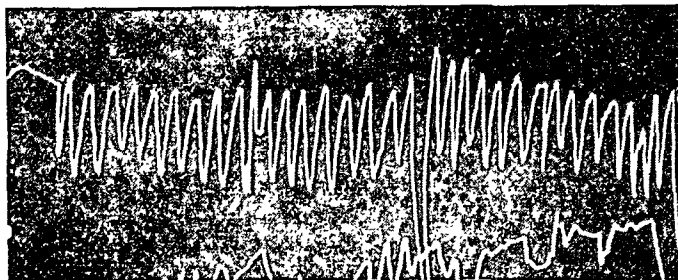


FIG. 2. Plethysmographic record of normal respirations between attacks.

Since none of the episodes was allowed to continue for more than five minutes at a time the rapidity of the onset and progress of the alkalosis may be easily judged. The urine gave an alkaline reaction with litmus paper during each episode and was acid in reaction during intervals. The alkalosis was due to an uncompensated carbon dioxide deficit consequent upon hyperventilation.

Kymo-roentgenographic and fluoroscopic studies were made and were the source of valuable information. In contrast to the rate of diaphragmatic contractions as demonstrated by the plethysmographic tracing (128 per minute) the kymograph roentgen-ray plate as viewed in the kymoscope picked up apparently isolated muscle bundle contractions as well as those of the entire organ and showed the contraction waves occurring at the rate of 155 per minute.

Following prolonged observation and study the patient was brought to operation. The phrenic nerves were resected by Dr. Andrew McQueeny under cyclopropane anesthesia. There were no reactions; the tic was immediately relieved and the patient is apparently cured.

DISCUSSION

Simonin¹ and Chavigny¹ in 1916 reported two cases of unusual diaphragmatic activity. They studied the cases for nearly three years and attached the

name "diaphragmatic chorea" to the syndrome. The contractions of the diaphragm in each of these cases were much slower than those reported subsequently by others, not exceeding 75 per minute. One case was thought to be purely hysterical and the other probably based on a previous pleurisy or pneumonia.

Gamble, Pepper, and Muller² observed in a case of post-encephalitic diaphragmatic tic that during the episode of rapid fluttering of the diaphragm rapid respiration brought about hyperventilation of the lungs with a resultant change in the CO_2 concentration in the blood and a marked alkaline reaction of the urine to litmus paper. In the quiescent state the CO_2 concentration was within normal limits and the urine acid in reaction. Section of the phrenic nerves brought relief.

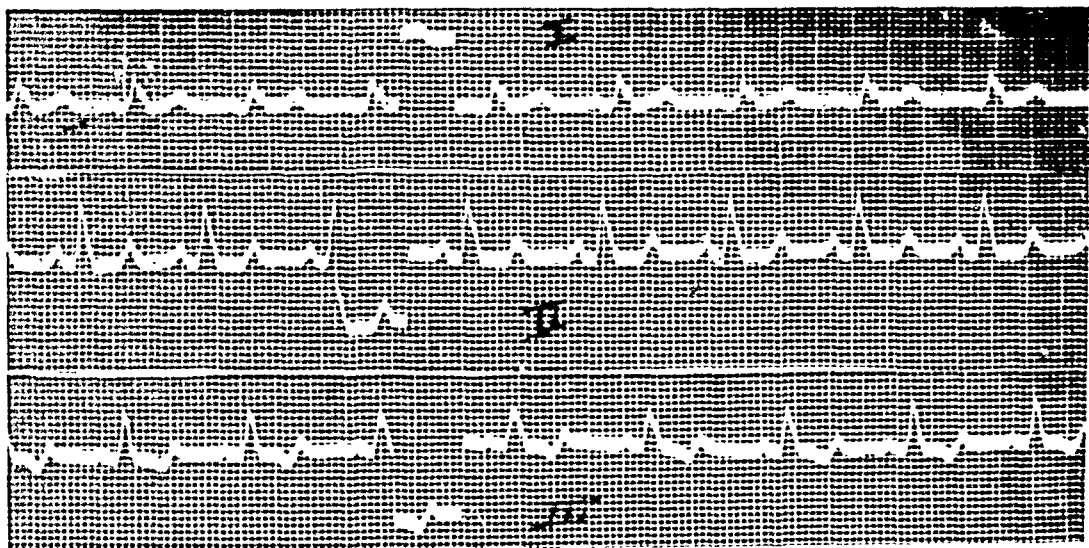


FIG. 3. Electrocardiogram taken during tic showing R-waves slurred and notched in Lead I. T-waves diphasic in Lead III.

W. A. Smith³ in 1926 included diaphragmatic tic among the respiratory disturbances following epidemic encephalitis. At the same time Kulenkamp⁴ described a fibrillary action of the diaphragm following an attack of influenza which he thought to be of central origin and classified it as a post-encephalitic muscular tremor. Downman⁵ in 1927 described a case in which the tic was bilateral and was relieved temporarily by freezing the phrenic nerves with ethyl chloride. More permanent relief was later obtained by sectioning both phrenics. Speirs brought out the important observation that avulsion of both phrenic nerves should be done in order to effect permanent relief. Simple section is followed in a variable length of time by nerve regeneration and a return of the original disturbance. Speirs'⁶ patient, after having bilateral avulsion of the nerves done, was entirely symptom free 18 months following operation.

Skilern⁷ and Green¹⁰ reported relief following avulsion of the phrenic nerves and the former concurred in the opinion of Speirs that permanent cure could be effected only by avulsion. He pointed out that from three to nine months following section the nerves were regenerated and the tic returned. He

also made note of the fact that re-operation on the phrenic nerves was attended with no little difficulty because the regenerated nerve was so much smaller and more difficult to find than the normal nerve. Lurje and Stern⁸ wrote at some length on the occurrence, the reference and the clinical significance of the pain associated with abnormal contractions of the diaphragm. They noted the severe type of thoracic pain referred to the left shoulder and arm simulating the pain of angina pectoris. They stressed the observation that the pain was not primarily of cardiac origin but was wholly due to a very evident dysfunction of the diaphragm. They named the condition the "cardiodiaphragmatic syndrome." Any cardiac dysfunction noted was due entirely to the mechanical ballottment of the heart by the upwardly moving diaphragm.

Roemheld,⁹ in discussing the work of Lurje and Stern, described a condition named by him the "gastrocardiac syndrome" and pointed out that the pain of angina pectoris may be simulated exactly by functional disturbances arising in the stomach and bowel. Green¹⁰ in the same year reported a case following encephalitis in which a cure was effected by resection of the phrenics.



FIG. 4. Plethysmographic tracing with belt around body at level of umbilicus.

Winkler¹¹ and Hoffbauer¹² in 1932 discussed the various degrees of severity of diaphragmatic tic and dwelt principally on the relation of diaphragmatic spasm to the occurrence of the pain of angina pectoris. They feel very definitely that there is some relationship between the anginal pain induced by coronary spasm or coronary sclerosis and the very same type of pain induced by diaphragmatic spasm.

To cite an instance wherein it has been observed that not all cases of diaphragmatic tic are either sequelae of epidemic encephalitis or associated with circulatory or alimentary disturbances, Karelitz¹³ in 1932 reported two cases of unilateral diaphragmatic spasm in infants, associated with cardiospasm and hypocalcemia. These cases were quickly and permanently relieved by calcium therapy.

In addition Gill and McArdle¹⁴ in 1934 reported two cases of pseudo-tympanites caused by hysterical spasm of the diaphragm. Both of these cases were cured by suggestion and manipulation—simple massage of the abdomen being sufficient to relieve the distention.

Two groups of interesting cases have been reported by H. Smith¹⁵ and by Porter.¹⁶ Both describe cases of diaphragmatic tic not related to previous acute

infectious illnesses and both relieved by resection of the phrenic nerves. One of Smith's cases is unusually interesting in that it presents the same possible causal factor demonstrated in the case being reported in this paper. Smith's case was operated upon five times for intestinal obstruction due to adhesions. My patient had also been operated upon five times, once for pyloric stenosis and the four succeeding times for obstruction due to adhesions. Porter's case is distinguished by the typical anginoid distribution of pain. In my patient the distribution of pain was confined to the epigastrium and left scapular region—the latter being the area in which pain is noted when the central cut end of the left phrenic nerve is stimulated by a faradic current. Porter is of the opinion that there are functional disturbances of the diaphragm that produce a syndrome very closely resembling angina pectoris due to coronary artery disease.

It might be apropos of these last cases mentioned, together with the case here reported, to inject into the discussion the opinions of Jackson and Jackson.¹⁷ These authors, after extensive experimental and clinical observations on angina pectoris and related symptoms come to the following conclusions: "Electrical stimulation at certain points inside the esophagus produces pain in those areas of the body in which the pain of angina pectoris and coronary thrombosis is felt." They believe the pain to be ipse-lateral and not to originate in the heart." They also believe that the coronary artery spasm explanation of angina pectoris is erroneous. They further feel that angina pectoris is caused by "incoördinated spasmodic contractions of the esophagus and stomach when gas or solid contents are entrapped under pressure within their walls; and that the cause of sudden death in angina pectoris is due to excessive vagus inhibition."

SUMMARY

A case of diaphragmatic tic, unassociated with a preceding history of epidemic encephalitis, influenza or other acute infectious illness has been described. It occurred in a woman of the hypopituitary and hypoadrenal type who presented a marked degree of hypotonicity of the entire gastrointestinal tract and had previously been subjected to multiple abdominal surgical procedures, the majority of which were concerned with relieving bowel obstruction due to adhesions. Possibly the presence of new adhesions between gastrointestinal tract and diaphragm may have had some irritative effect upon the diaphragm, inciting it to contract clonically whenever food is passed into the stomach.

Most of the cases reported have had associated pain of anginoid type and distribution. Resection or avulsion—preferably the latter—of both phrenic nerves offers the only complete and permanent cure. There are no contraindications to such procedures and there have been no permanently distressing results following operation. Considerable pain is felt in both shoulder regions for several weeks after operation. This is not disabling and soon passes away.

REFERENCES

1. SIMONIN: Chorea of diaphragm, Paris méd., 1916, vi, 191.
CHAVIGNY: Chorea of diaphragm, Paris méd., 1916, vi, 191.
2. GAMBLE, C. J., PEPPER, O. H. P., and MULLER, G. P.: Post-encephalitic tic of diaphragm, Jr. Am. Med. Assoc., 1925, lxxxv, 1485-1487.

3. SMITH, W. A.: Respiratory disturbances following epidemic encephalitis, *Arch. Neurol. and Psychiat.*, 1926, xv, 617.
4. KULKENKAMP, G.: Tremor of diaphragm following influenza, *Deutsch. Ztschr.*, 1926, xciv, 312-314.
5. DOWMAN, C. E.: Relief of diaphragmatic tic following encephalitis by section of phrenic nerves, *Jr. Am. Med. Assoc.*, 1927, lxxxviii.
6. SPEIRS, G. O.: Encephalitic diaphragmatic spasm relieved by phrenectomy, *Jr. Nerv. and Ment. Dis.*, 1929, lxi, 407-413.
7. SKILLERN, P. G.: Tic of diaphragm relieved by resection of phrenic nerves, *Jr. Am. Med. Assoc.*, 1931, xcvi, 2098-99.
8. LURJE, S. J., and STERN, B. M.: Connection of cardiophrenic syndrome and collection of air in left hypochondrium, *Ztschr. f. klin. Med.*, 1931, cxv, 552-569.
9. ROEMHELD, L.: Discussion of cardiophrenic syndrome, *Ztschr. f. klin. Med.*, 1932, cxix, 541-544.
10. GREEN, B.: Division of both phrenics for relief of spasm of diaphragm following encephalitis, *South. Med. Jr.*, 1932, xxv, 392-394.
11. WINKLER, F.: Cardiac pain and relation to diaphragmatic angina, *Wien. med. Wchnschr.*, 1933, lxxxiii, 447-450.
12. HOFFBAUER, L.: Angina pectoris diaphragmatica, *München. med. Wchnschr.*, 1933, lxxx, 411-415.
13. KARELITZ, S.: Unusual manifestations of tetany, cardiospasm and unilateral diaphragmatic spasm, 1932, *Libman Anniversary Vol. No. 11*.
14. GILL, W. G., and McARDLE, M. J.: Two cases of pseudotympanites caused by hysterical spasm of diaphragm, *Guy's Hosp. Rep.*, 1934, lxxxiv, 94-99.
15. SMITH, H.: Diaphragmatic tic relieved by section of phrenic nerves, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 837-840.
16. PORTER, W. B.: Diaphragmatic flutter with symptoms of angina pectoris, *Jr. Am. Med. Assoc.*, 1936, cvi, 992-994.
17. JACKSON, D. E., and JACKSON, H. L.: Experimental and clinical observations regarding angina and some related symptoms, *Jr. Lab. and Clin. Med.*, 1936, xxi, 993-1006.

HYPERINSULINISM DUE TO ADENOMA OF THE ISLETS OF LANGERHANS: CASE REPORT WITH METABOLIC STUDIES BEFORE AND AFTER REMOVAL OF TUMOR*

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At the present time, the comparative rarity of cases of adenoma of the islets of Langerhans and the short time which has elapsed since the discovery of the condition and of its clinical significance, render each case of extreme interest to the medical men concerned in its diagnosis and in the discovery and removal of the tumor at operation. Moreover, our knowledge of the condition is still in the stage when it can be furthered by careful studies in any given case.

Shortly after Banting and Best² announced their discovery of insulin in 1922 the clinical syndrome associated with hypoglycemia due to overdosage of this

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hormone was observed. One year later Seale Harris¹⁰ suggested the clinical possibility of hyperinsulinism, analogous to hyperthyroidism, as the cause of hypoglycemic symptoms occurring in individuals not taking insulin. In 1927 Harris's hypothesis became a fact when the first case of hyperinsulinism associated with a tumor of the pancreas was reported by Wilder et al.²¹ The tumor proved to be a carcinoma of the islet tissue with metastasis to the liver, and from the metastatic nodules there was obtained a substance which proved to have an insulin-like action when injected into rabbits. In 1929 the first surgical cure of hyperinsulinism was reported by Howland et al.¹² of Toronto, Roscoe Graham removing from the pancreas a small circumscribed tumor which was a slow-growing carcinoma of the islets. This series of events thus led up to the beginning of a new chapter in surgery of the endocrine system which is now but 10 years old.

It is not our intention to review the already voluminous literature on the subject as this has been done well by several authors such as Whipple and Frantz (1935),²³ Womack (1937)²⁵ and Whipple (1938)²² and a perusal of one or all of these articles would well repay anyone interested in the subject. It was felt, however, that it might be of interest to bring the reported cases up to date, using the last figures by Whipple up to the end of 1937 as the basis of this undertaking. Of the total of 56 cases listed by Whipple in which operation was undertaken and a tumor found are 43 cases in which the tumor was an islet-cell adenoma. Up to December 1939 an additional nine such cases have appeared in the literature. They are those reported respectively by Åkerberg,¹ Parade and Kindler,²⁰ Fraser, Maclay and Mann,⁸ Hermannsen and Nestmann,¹¹ Nicholson and Hart,¹⁰ Krauss,¹⁶ West and Kahn²¹ and Duncan, Hayward and Flick⁶ (2). The present case thus brings the number up to 53. These additional cases recovered satisfactorily from their operations with the exception of that reported by Hermannsen and Nestmann,¹¹ their patient having contracted a hypostatic pneumonia which resulted in death four days after operation. Jirasek and Postranecky¹³ have also reported a case but this appears to be the last one included in Whipple's list under "personal communication." In the case reported by Forbes, Davidson and Duncan⁷ no tumor was found at operation, a portion of the pancreas was resected and in it a small encapsulated adenoma was found, the operation having the same successful outcome as those in which adenomata have been found and enucleated. Levison and Ramsey¹⁷ report a case in which the pancreas was explored and no tumor found; the patient died suddenly on the fifth postoperative day and at autopsy an encapsulated adenoma measuring 1.5 cm. in diameter was found in the tail of the pancreas. In the second case reported by West and Kahn²¹ the body and tail of the pancreas were removed following failure to find a tumor. The patient died after a short postoperative period during which there was a return of symptoms. At autopsy an islet-cell adenoma was found behind the second portion of the duodenum just proximal to the ampulla. In Bergonzi's case⁸ operation was advised; this was eventually done under local anesthesia, resulting in the surgeon having to limit himself to manual exploration of the pancreas. The patient died in coma 24 hours later and at autopsy there was found an islet-cell adenoma at the point where the body of the pancreas passes into the tail. Two cases are reported, one by Jones and Matte¹⁴ and the other by Malamud and Grosh,¹⁸

where the patient died before operation was undertaken and at autopsy an islet cell adenoma was found in the pancreas.

Whipple²² reported 34 cases where partial resection of the pancreas was carried out in view of failure to discover a localized tumor. On 27 of the 30 surviving cases sufficient data were assembled to warrant the statement that 10 were relieved of their symptoms, 4 were improved and 13 were unimproved. To this type of case can be added that of Clarke⁴ who resected 35 grams of pancreatic tissue after splenectomy was performed, the patient as a result being 'greatly improved.'

It is of interest that of the 15 cases of islet-cell tumor, referred to above, the reports of which have appeared in the literature since Whipple's list was compiled at the end of 1937, there was not one instance of carcinoma, each being a simple adenoma, whereas there were no less than 13 carcinomata among the 56 cases reported by Whipple.

CASE REPORT

M. M., a white married woman, aged 43, had been in good health until seven years ago, when she developed attacks of weakness, faintness and double vision when playing golf. She soon found that relief was obtained in five to ten minutes by eating candy or drinking orange juice.

TABLE I

ORAL GLUCOSE TOLERANCE TESTS

Blood sugar values determined after the oral administration of 100 grams of glucose

Fasting		Time in Hours				
		1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.
Blood sugar in mg. per 100 c.c.	84	114	Preoperative (Oct. 17, 1938) 110 80			50
	102	214	Postoperative (Dec. 21, 1938) 180 174		120	96
	102	92	Postoperative (March 27, 1939) 92 94			104

The attacks became more frequent, occurring at night, upon awakening, after exertion and between meals. Her physician advised her to eat frequently, but she continued to have episodes of weakness, incoherent speech, sweats, headaches, hunger, blurred vision and lapses of memory lasting from a few minutes to several hours.

During the past two years there had been changes in her personality, these causing the greatest concern to her relatives and friends. She threw her favorite flower vases against the fireplace and tore up her letters without reading them. In her lucid intervals she had no recollection of her extraordinary behavior.

In the past year a physician placed her on a high fat diet with frequent feedings, which seemed to decrease the frequency of attacks, but she gained 35 pounds in seven months.

Upon admission to the Santa Barbara Cottage Hospital on October 13, 1938, the patient was in a semi-stuporous and confused state, responding incoherently to ques-

tions. She was promptly relieved by a glass of orange juice. Physical examination revealed nothing significant except overweight. A tentative diagnosis of hypoglycemia was made.

During two weeks of observation eight fasting blood sugar determinations varied from 40 to 84 mg., and averaged 54 mg. per cent. Urinalysis, blood counts, Wassermann test, basal metabolic rates, liver function tests, and roentgen-rays of skull gave normal results. The ordinary Ewald showed 0° free HCl and 8° total acidity. Her weight taken during this time was 160 pounds.

ORAL GLUCOSE TOLERANCE TESTS

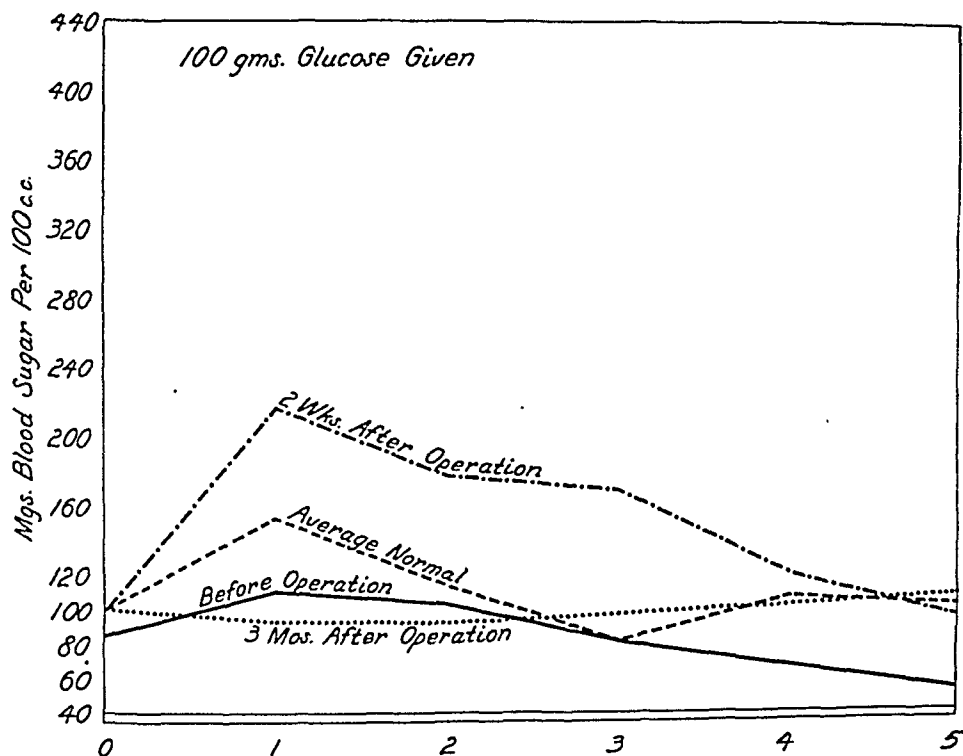


CHART 1. Graphic representation of the blood sugar values shown in table 1.

Glucose and insulin tolerance tests before operation revealed significant data.

The oral glucose tolerance test (table 1 and chart 1), using 100 grams of glucose and carried on for five hours, showed a flat type of curve which is found in hyperinsulinism. During the fifth hour when the blood sugar was 50 mg. per cent the patient showed definite signs of weakness and confusion, which were relieved by 200 c.c. of orange juice. This curve deviates from normal in that at the end of three hours the blood sugar continued to fall and at the end of the fifth hour the level reached was low compared with that of the fasting blood sugar.

The intravenous glucose tolerance test (table 2 and chart 2), using 100 grams of glucose administered at a constant rate by the electrically driven pump* designed by one of us (A. E. K.) over a period of 2 hours, showed a marked fall of the blood sugar at the end of two and one-half hours. The fall to 34 mg. per 100 c.c. of blood was associated with severe weakness and mental confusion and was probably due to the stimulation of a powerful insulin secreting mechanism. In this case the intra-

*A description of the apparatus has been accepted for publication by the Journal of Laboratory and Clinical Medicine.

TABLE II

INTRAVENOUS GLUCOSE TOLERANCE TESTS

Blood sugar values determined after the intravenous administration of 100 grams of glucose at a constant rate over a period of 2 hours

Fasting		Time in Hours									
		½	1	1½	2	2½	3	3½	4	4½	5
	56		176	176	152	34	Preoperative (Oct. 21, 1938)				
	104		358	408	418	242	Postoperative (Dec. 27, 1938)				
	106		252	282	374	310	Postoperative (March 30, 1939)				
							156	96	82		

venous glucose tolerance test brought about a greater lowering of the blood sugar. In cases so far studied, this seems to be the rule and consequently the intravenous test appears to be of greater value than the oral as a diagnostic test for the presence of excessive amounts of insulin.

The intravenous insulin tolerance test (table 3 and chart 3), which consisted of the administration of 2 units of insulin in 200 c.c. of normal saline over a period of

INTRAVENOUS GLUCOSE TOLERANCE TESTS

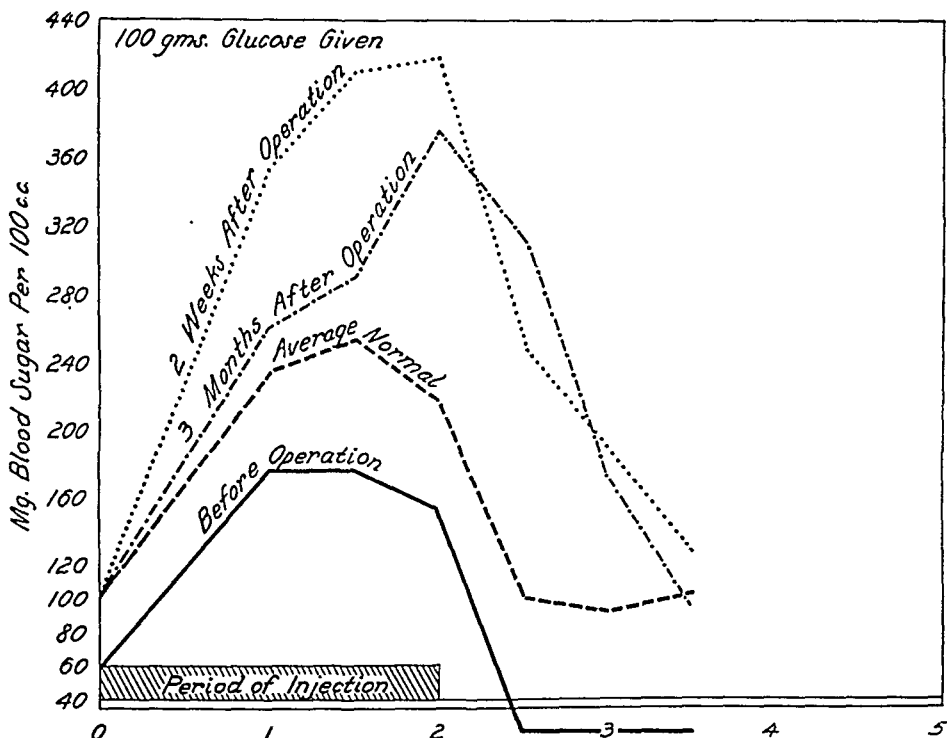


CHART 2. Graphic representation of the blood sugar values shown in table 2.

TABLE III

INTRAVENOUS INSULIN TOLERANCE TESTS

Blood sugar values determined after the intravenous administration of 2 units of insulin at a constant rate over a period of 2 hours

Fasting		Time in Hours											
		½	1	1½	2	2½	3	3½	4	4½	5	5½	6
Blood sugar in mg. per 100 c.c.	50		44	44	40	Preoperative (Oct. 27, 1938)							
						46	44						
	112	96	88	88	88	Postoperative (Dec. 24, 1938)							
						108	108						
	104		102	92	96	Postoperative (March 28, 1939)							
						96	96	104					104

two hours with the Koehler constant-rate pump showed a minimal lowering of the blood sugar level and an absence of the usual spontaneous recovery at the end of 3 hours. The patient remained drowsy throughout the period of this test.

Because of the history of prolonged severe hypoglycemic symptoms, associated with repeated low fasting blood sugars, glucose tolerance curves showing evidence of an excessive supply of insulin in her body, a poor hypoglycemic effect from insulin

INTRAVENOUS INSULIN TOLERANCE TESTS

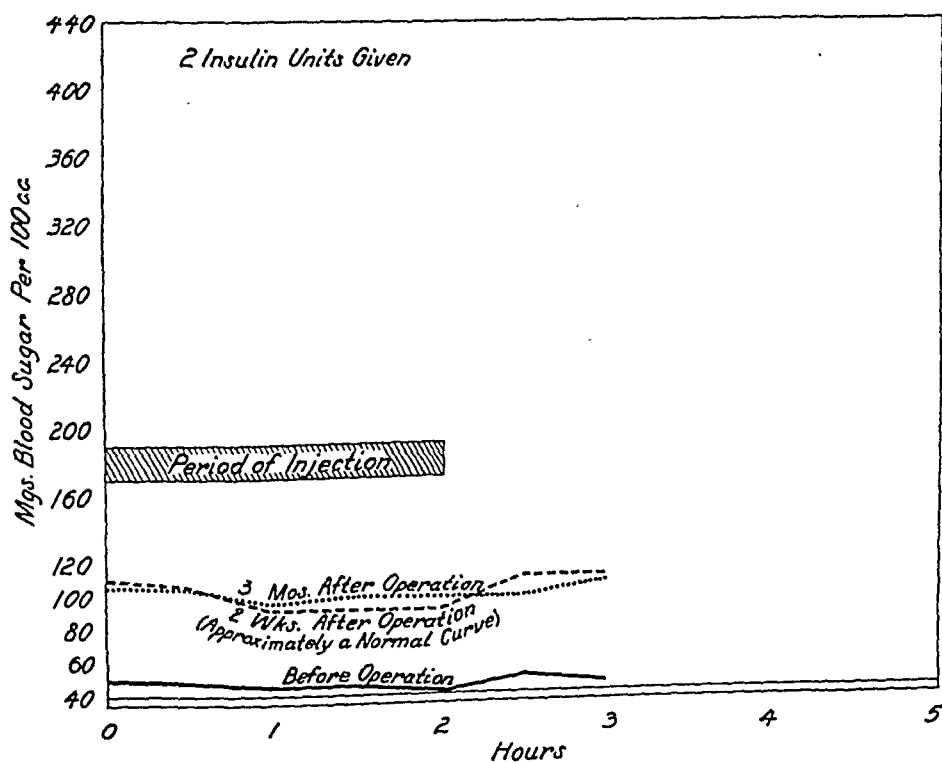


CHART 3. Graphic representation of the blood sugar values shown in table 3.

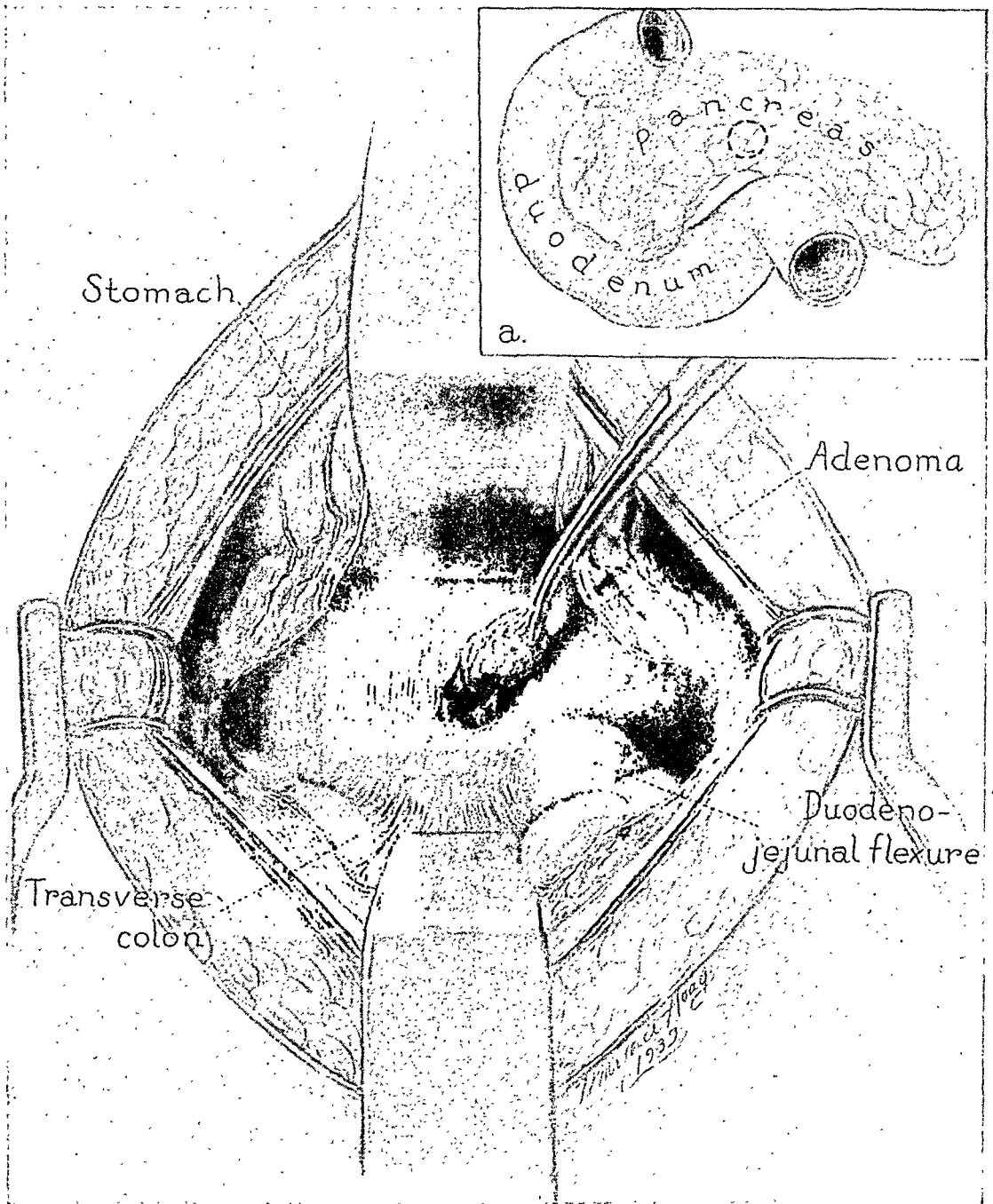


FIG. 1. Drawing to illustrate the actual removal of the adenoma from the pancreas. The inset shows the position of the tumor in the gland.

given intravenously, and little or no relief from dietary treatment, a diagnosis of probable tumor of the islets of Langerhans was made. An exploratory operation was advised, but the patient decided to return home a while before having this done. She was given a high fat diet with a ratio of two parts of fat to one of carbohydrate, six feedings daily, using a protein sandwich at bedtime. On this program she continued

to have attacks of hypoglycemia, but they were not so severe. After remaining at home for five weeks, during which time she lost three pounds in weight, she returned to the hospital for abdominal exploration which was done by one of us (J. H. S.) on December 8, 1938. It was of interest that after using a high fat diet for one month the highest fasting blood sugar was obtained, namely 93 mg. per cent. This is in accordance with the experience of many that the use of a high fat diet diminishes the tolerance for glucose.

Operation: December 8, 1938. General anesthetic of nitrous oxide, oxygen and ether administered through the intra-tracheal route. A left paramedian incision was made extending from the costal margin above to a point about $1\frac{1}{2}$ inches below the level of the umbilicus, the fibers of the rectus abdominis muscle being split vertically. The peritoneal cavity was then opened and a general exploration made during which no pathologic condition was noted. An excellent exposure of the pancreas was obtained through the omental bursa which was entered by incising the two anterior layers of the gastro-colic omentum along a line parallel to the greater curvature of the stomach and sufficiently distant from it to avoid injury to the gastro-epiploic artery. The gland had a normal appearance, no tumor being visible, nor was there present any nodularity suggestive of a tumor in its substance. On careful palpation, however,

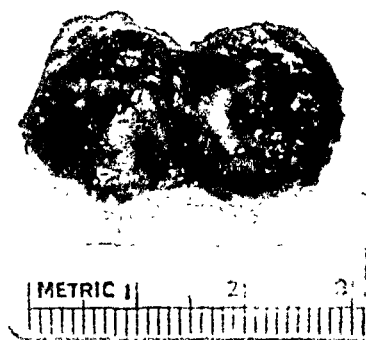


FIG. 2. Photograph of bisected tumor.

there was found an area of slightly harder consistence than the normal pancreatic tissue, about 2 cm. in diameter and situated just above the lower border of the gland at the junction of the body with the head (figure 1). As this was the only area which gave rise to hopes of possible pathologic findings, further exploration was decided upon. The peritoneum was incised along the lower border of the pancreas in this region and a finger insinuated under its inferior surface immediately above the terminal portion of the duodenum. Palpation between finger and thumb now left no doubt as to the presence of a small nodular tumor in the substance of the pancreas. Enucleation was undertaken by tearing gently through the glandular tissue anterior to the tumor followed by blunt and gauze dissection. As this dissection proceeded, the tumor became more distinguishable from the surrounding pancreatic tissue, being of a grayish-red color, and the final stages of its enucleation were accomplished with such ease as to indicate that, on its posterior aspect at least, it was definitely encapsulated. The tumor (figure 2) was somewhat spherical in shape, about 2 cm. in diameter and, on being bisected, consisted obviously of a tissue differing entirely, both in appearance and consistence, from the pancreas in which it had been buried. During the dissection there was a surprising amount of hemorrhage considering the small

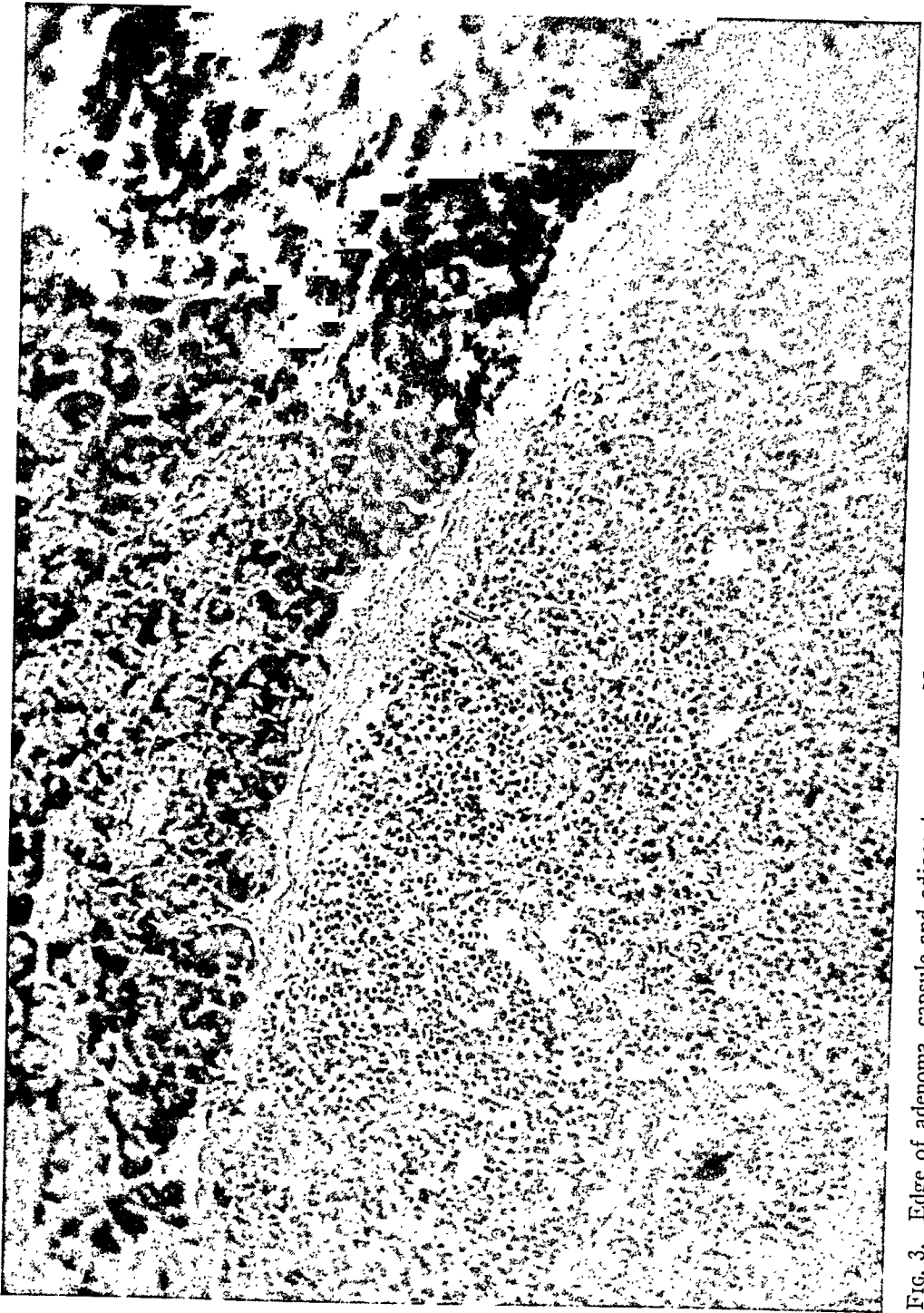


FIG. 3. Edge of adenoma, capsule and adjacent pancreas. Note the similarity in staining reaction and relative size between the tumor cells and those in the adjacent islet. H and E. $\times 280$.

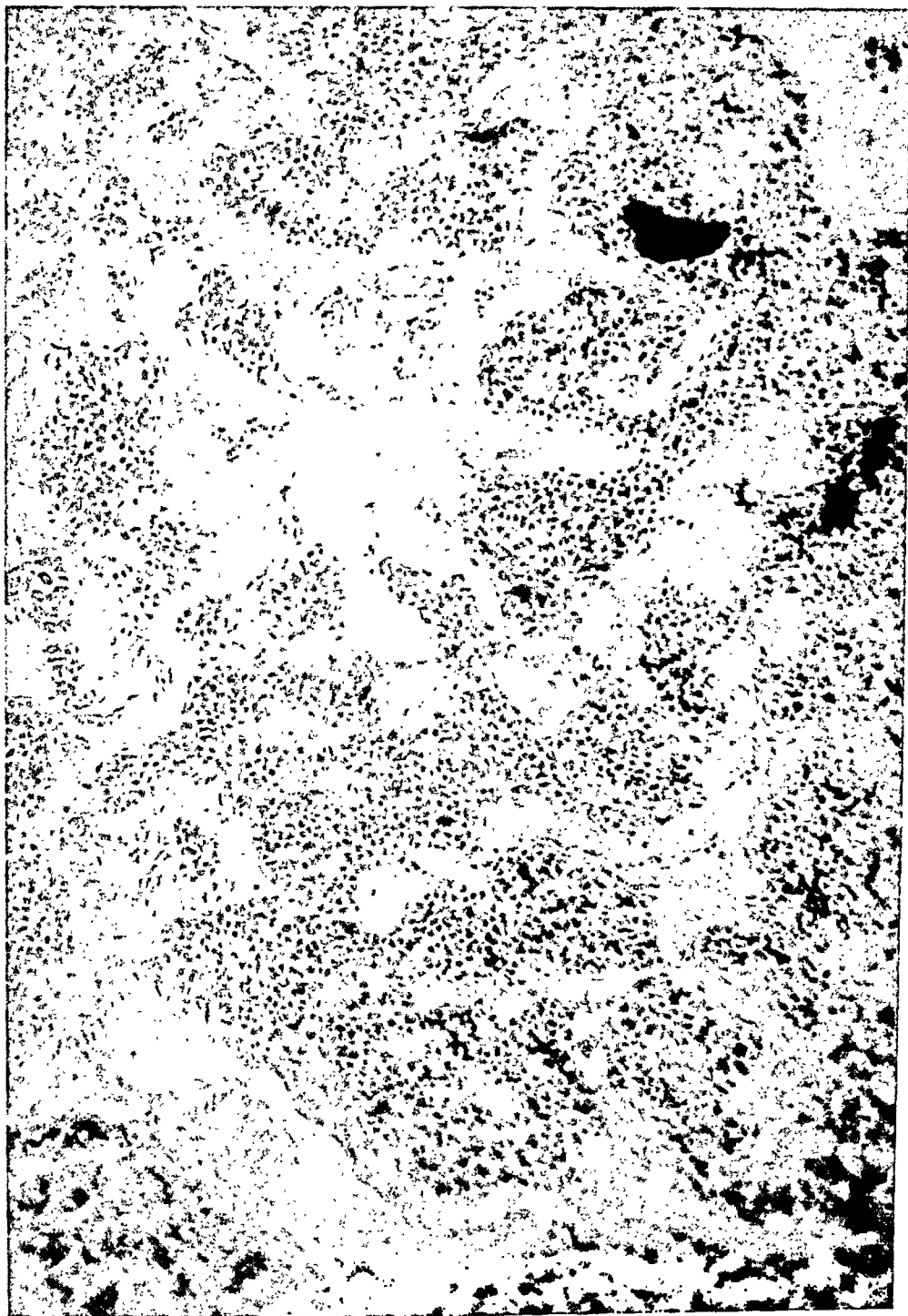


FIG. 4. Area of tumor where stroma is sparse and highly vascular. Hyaline tissue about the capillaries is conspicuous.
H and E. $\times 280$.

amount of damage done to the pancreas. When the bleeding points had been ligatured with thin silk, it was found that the pancreatic tissue had bulged into, and almost obliterated, the small cavity incident upon the removal of the tumor, so that only a couple of silk sutures sufficed to complete its closure. A further careful palpation of the pancreas failed to reveal any other suspicious areas. The pancreatic area of operation was not drained as there appeared to be no indication for such a procedure and, after the incision in the omentum had been repaired, the abdominal wound was closed in layers.

At the end of the operation the patient's condition was very good for, after an anesthesia lasting nearly two hours, her blood pressure had not altered and her pulse had risen only 10 beats per minute.

Post-operative course: During the operation and for the following 24 hours the patient was given intravenous saline only so that the administration of glucose played no part in the remarkable changes which took place in her blood sugar values, these apparently being the result of the removal of the tumor, since any changes which might be attributable to the operative procedure or anesthetic would be only temporary and of a minor character. As will be seen from chart 4 there was a well marked transient hyperglycemia, the blood sugar rising to 270 mg. per 100 c.c. some 8 hours after operation. On the third day following operation the fasting blood sugar was found to be within normal limits and remained so during the remainder of her stay in the hospital.

The patient made a perfectly straightforward recovery, the wound healing by first intension. She was allowed up on the twelfth day following her operation and, when standing for the first time, she was so amazed at the disappearance of the uncertain "billovy" feeling which had haunted her so long that she became overcome with emotion. She was also delighted to find that she could now see plainly the nearby mountains which, during her previous sojourn in the hospital, had always appeared blurred. On her twentieth postoperative day she left the hospital feeling well enough to undertake the long journey to her home.

To Dr. Clark Brown, Pathologist to the Santa Barbara Cottage Hospital, we are indebted for the following report on the tumor:

Gross: Specimen consists of a section of pancreas measuring 2 by 2 by 2 cm. In its center is a nodule of fleshy, gray, hemorrhagic tissue 1.5 cm. in diameter. This is distinct from the surrounding lobulated pancreatic tissue and appears to have a thin capsule. The total weight of the specimen is 1.952 gm. of which 1.304 gm. is tumor tissue and the remainder pancreas.

Microscopic: The nodule is composed of coils and clusters of large cells distinctly lighter than those of the adjacent acinar cells, and resembling cells of the islets (figure 3). The nodule is surrounded by a well-defined though imperfect fibrous capsule. Through broad defects in the capsule blunt projections of tumor contact the acinar cells directly. The supporting structure of the tumor cells is composed of sparse, fine connective tissue strands and abundant capillaries. Capillaries bound cords of tumor cells on most sides. In places the tumor cells form the walls of the vascular channels without the interposition of an endothelial lining (figure 5). This appearance, however, may be due to traumatic hemorrhages. The tumor cells (figure 8) are apparently of three varieties. Granular material could be identified in practically all cells stained with Bensley's modification of Mallory's aniline blue stain. The most predominant cells are moderately large with closely-packed fine blue granules resembling the beta cells. These cells are often of a cuboidal or columnar shape, but frequently they appear crowded into triangular or stellate shapes as they are molded about large, pale, round cells. The second type of cells, and possibly a transition phase of the first, are larger, round and smooth. They contain fine blue granules similar to those in the first cell type which are widely scattered, giving the cell a pale

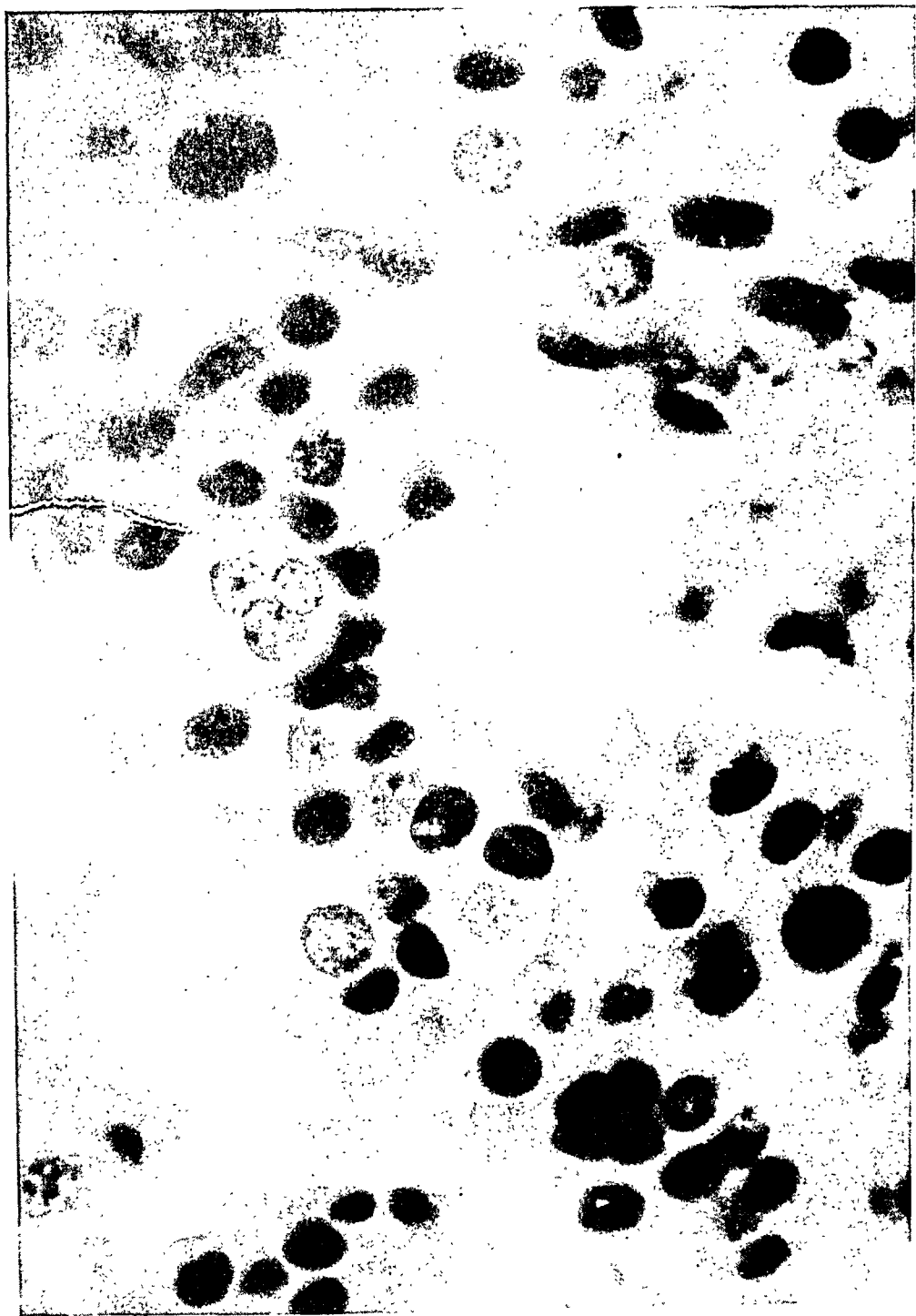


FIG. 5. Note the large round clear cell with multiple nuclei. With modified Mallory's aniline blue stain the cytoplasm contains scarce, pale blue granules: these cells, if they were compressed, might resemble those of the beta type. Red cells are seen lying immediately adjacent to the cords of tumor cells. H and E. $\times 2520$.

appearance. This pale cell type coincides with descriptions of duct epithelium, but its cytoplasmic distinction from the beta cells appears to be quantitative rather than qualitative. In addition it tends to be multinuclear or to possess giant nuclei. The third cell type (alpha cells) has the moderate size of the first type but contains fairly large, reddish-orange cytoplasmic granules. It is less numerous than the other two

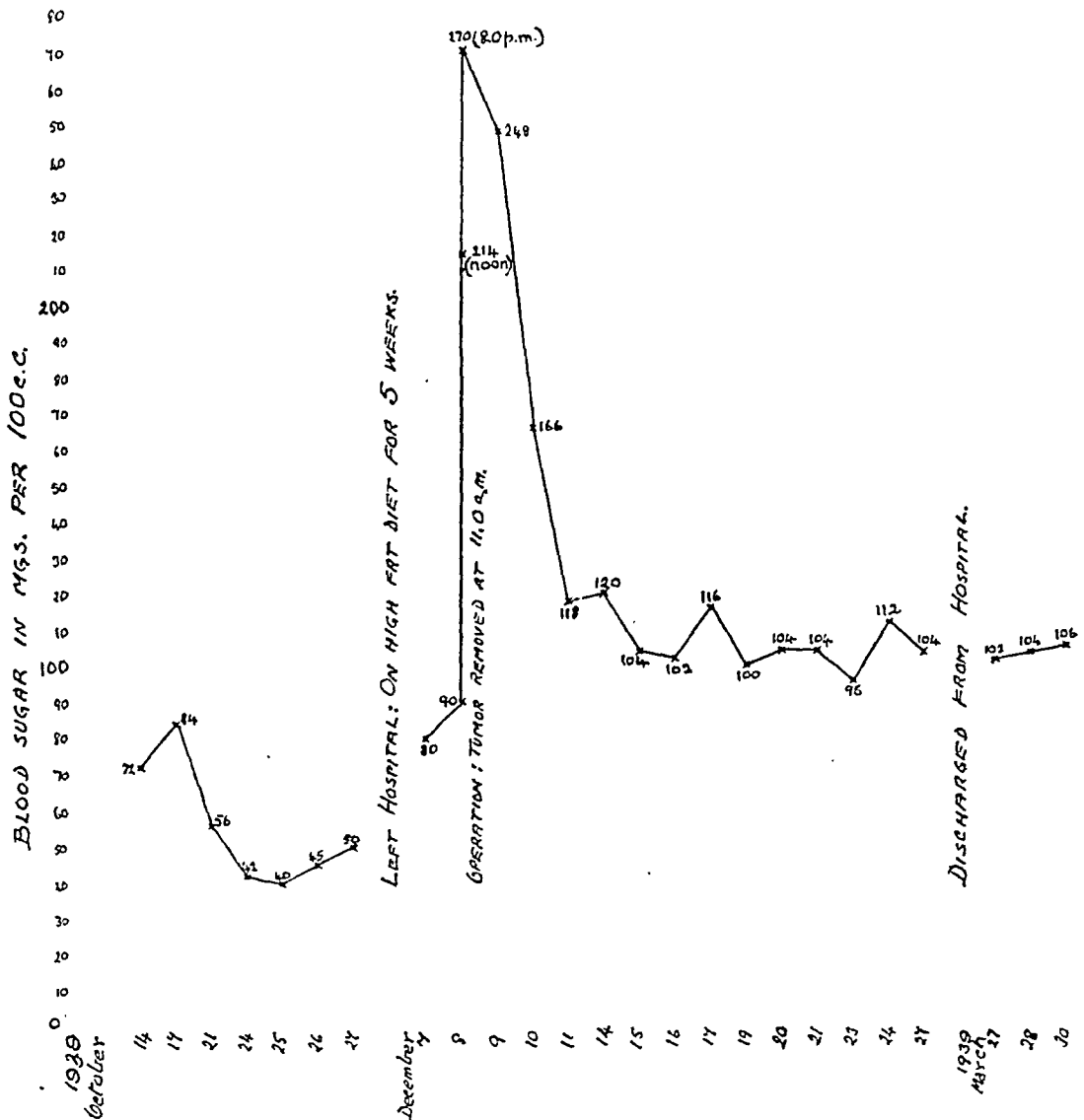


CHART 4. Graph to show (1) fasting blood sugar values during the patient's three periods in hospital, (2) marked transient hyperglycemia following removal of the tumor (uncomplicated by the administration of glucose), (3) permanent return, to within normal limits, of fasting blood sugar values 3 days after operation.

cell types. Mitotic figures are very rare in any of the cells. Extracellular hyaline material similar to that seen in the islets of diabetes and emphasized by Laidlow in islet tumors is deposited in parts of the tumor (figure 4).

Pathological diagnosis: Islet-cell adenoma.

Two weeks after operation, glucose and insulin tolerance curves were repeated. The oral curve (table 1 and chart 1) after the operation was markedly different from

that obtained previous to operation in that the fasting blood sugar was normal and the blood sugar at the end of the first hour (214 mg. per cent) was suggestive of a borderline diabetes and is probably accounted for by an incomplete readjustment of tolerance to glucose following removal of the adenoma. However, at the end of five hours the blood sugar had returned to normal which is unlike its behavior in true diabetes. A trace of sugar was found in the first and second hour urine specimens.

The intravenous glucose tolerance curve at this time (table 2 and chart 2) showed a marked decrease in tolerance as compared with that before removal of the adenoma.

In the intravenous insulin tolerance test (table 3 and chart 3) it will be noted that the blood sugar values are maintained at a high level during the entire test in contrast to the low values obtained in the similar test before operation. The curve also differs from the pre-operative one in that a greater hypoglycemic effect is evident at the end of the first hour while at the end of the third hour the level of the blood shows a normal recovery.

At the end of three months after her operation the patient returned to the hospital for further metabolic studies. During this time there had been no return of her pre-operative symptoms; she weighed 147 pounds, representing a loss of 10 pounds since her operation, and was feeling very well.

During her short stay in hospital at this time the fasting blood sugar value was determined on three occasions and found to be respectively 102, 104 and 106 mg. per 100 c.c. of blood (chart 4).

Determinations of the blood sugar values after the oral administration of 100 gm. of glucose indicated a marked increase in tolerance as compared with similar determinations made two weeks after operation. While the failure of the blood sugar to rise might be interpreted as indicative of some degree of hyperinsulinism, yet the fact that she had remained free from symptoms up to this time, and has continued to do so, militates against this interpretation and leads one to suspect faulty absorption of the glucose as the more probable explanation. In fact, this explanation is supported by the intravenous glucose tolerance curve which indicates a return towards normal and shows a distinct gain in tolerance compared with the curve obtained two weeks after operation.

The insulin tolerance curve shows a spontaneous recovery at the end of three hours similar to the curve two weeks after removal of the adenoma.

In a letter written to us on January 1, 1940 the patient's husband states: "I have to advise you that my wife has enjoyed the best health the past year of many, many years. She has had no indication whatever of her old trouble, does not tire readily and only if she is up really late at night, then recovers quite readily from fatigue. She does her own house work and her weight varies between 140 and 145."

COMMENT

There does not seem to be any necessity to enter fully into the question of differential diagnosis of the cause of a hypoglycemia as the main points have been often discussed in previous articles on the subject. Perhaps it is enough, and would not be out of place, to reiterate that the diagnosis of islet-cell tumor cannot yet be made with absolute certainty but that it depends largely upon eliminating the other causes of hypoglycemia. However, the more case reports one reads the firmer grows one's impression that cases with very low blood sugar values and corresponding severe symptoms are more likely to be due to a hyperinsulinism consequent upon a tumor of the islets of Langerhans than to any other etiological factor. In other words, it would appear that other causes of hypoglycemia, such as diseases of the pituitary, adrenals, thyroid and liver are not

likely to produce the profound degree of hypoglycemia commonly found when a tumor of the islets is present. Furthermore, should disease of these other glands be advanced sufficiently to give rise to a severe hypoglycemia, then it is very probable that in such a case the etiological factor would be apparent.

Our small experience with the insulin tolerance test confirms that of Fraser et al., who state they found this test to be the most useful procedure for demonstrating the presence of hyperinsulinism in the case they reported. As shown in chart 3 before operation there is a poor initial effect of the intravenous insulin on the blood sugar, indicating slight sensitivity (that is, a high degree of tolerance) to the insulin. Another characteristic of this curve is the absence of spontaneous recovery after the injection of insulin had ceased, this feature probably being due to the activity of some continuously-acting insulin mechanism, and indicating the presence of more insulin than normal. After the removal of the tumor both these findings were reversed, the initial effect of the insulin being to lower the blood sugar level quite appreciably and spontaneous recovery took place after the injection of insulin ceased, the insulin mechanism apparently having been restored to normal.

From the fact that the insulin tolerance test has hardly ever been mentioned in case reports of islet-cell tumor, it is obvious that much work still remains to be done with regard to its standardization and interpretation. Collip⁵ recently postulated that the responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the subject's own gland. Gray and Burtneess⁹ carried out a series of insulin tolerance tests on hypoglycemic, normal and diabetic subjects, using 0.01 unit of insulin per kilogram of body weight, and their results appeared to lend support to the validity of this postulate. In this communication we are reporting a case of proved hyperinsulinism in which the insulin tolerance curves obtained also coincide with those which would be expected from Collip's postulate. Should the results of investigations in further instances of islet-cell pathology be found to conform to this postulate, then the insulin tolerance test may prove of specific value in the diagnosis of this condition even in its earlier and more obscure state. We know that in most cases of islet-cell adenoma the history is a lengthy one with gradual increase in the severity and frequency of attacks, the probable diagnosis usually only having been made when severe symptoms had already been present for some time. While at present this is in itself an achievement, yet it would naturally be desirable to be able to make the diagnosis before symptoms have become severe. Hence we feel that if the insulin tolerance test can be proved reliable as a means of demonstrating the presence of hyperinsulinism, which is the cause of the hypoglycemia in these cases, then a definite step forward in diagnosis will have been made. We therefore make a plea for the more frequent performance of this test in cases of hypoglycemia on the grounds that it merits thorough investigation and that its value cannot be assessed except by this means.

So far as the relative values of the oral and intravenous glucose tolerance tests are concerned, the work of Koehler and Hill¹⁵ has shown that due to the variation in both rate and amount of absorption of glucose when given by mouth, the intravenous method of administration gives results more indicative of the true ability on the part of the body to metabolize glucose. Our pre-operative findings in the present case demonstrate specifically that the intravenous test showed more strikingly the hypoglycemic tendency than did the oral while after

removal of the adenoma we think it probable that the intravenous test again revealed more accurately the true condition than did the oral, the findings of the insulin tolerance test and the freedom from symptoms of the patient both helping as evidence in support of this opinion.

It has been estimated that the amount of islet-cell tissue present in a normal pancreas is about 2.5 per cent of the whole gland. Taking 90 grams as the weight of the average pancreas, then the islet-cell tissue in such a gland would weigh approximately 2.25 grams. The weight of the adenoma removed in this case was 1.304 grams, representing an increase in insulin-secreting tissue of nearly 60 per cent above the normal amount. These figures, although necessarily only approximate, serve to indicate why such a small tumor should have given rise to such a marked metabolic disturbance.

There is no doubt that when the pancreas is to be explored for a possible islet-cell tumor an adequate exposure of the whole of the gland is essential. These tumors have been found in both extreme lateral limits of the pancreas and therefore the whole of the gland should be exposed in anticipation that one may have to work in either or both of these regions, although one always hopes that the fates will have been kind enough to arrange for the tumor to be situated in a more readily accessible portion of the gland, as in the present instance. The knowledge, too, that on occasions more than one tumor has been found in a pancreas further renders adequate exposure essential.

In the present case a long left paramedian incision was used, with splitting of the rectus abdominis muscle in the direction of its fibers. We have long felt that most operative procedures in the upper abdomen can be done comfortably through a paramedian incision, the choice of side depending upon the procedure to be undertaken, and it was found to answer our purpose admirably in this case. Whipple uses a transverse epigastric incision, with transverse division of both recti muscles, for his operations on the pancreas. He makes the point that in cases where it is deemed necessary to explore the head of the pancreas, this can only be done efficiently by mobilizing the duodenum and, since to do this it is necessary to incise the peritoneum along the right border of this part of the gut, it is essential to secure a good exposure in this direction. However, we think that if, in the present case, we had felt the necessity of thus exploring the head of the gland, the incision used would have been found to be adequate enough for this purpose.

The question of whether or not a partial resection of the pancreas should be done after failure to find a tumor is one which will always gravely exercise the mind of the surgeon, for the presence of islet hyperplasia or hypertrophy, which might conceivably be giving rise to hyperinsulinism, cannot be determined by palpation. We know that in the majority of cases in which this has been done the results have not been satisfactory yet, on the other hand, not only has it been successful in a few cases which apparently would not have been benefited otherwise but in one case, that of Forbes, Davidson and Duncan,⁷ the resected portion of the pancreas actually contained an adenoma which the surgeon has been unable to find when exploring this gland. Consequently we feel one cannot be dogmatic about the answer to this question for it is obvious that each case must be considered on its own merits both medical and surgical, but it might be added that pre-operative evidence of the presence of hyperinsulinism would

render the procedure more justifiable and even advisable. In retrospect it would indeed be interesting could we have known the status of this condition, as determined by insulin tolerance tests, in those cases which received benefit from partial pancreatectomy and in those which did not. West and Kahn's second case²¹ and that reported by Levison and Ramsey,¹⁷ in each of which an adenoma was found at autopsy shortly after failure to discover it at operation, serve to remind us that, unless the exploration of the head and tail of the pancreas, the most difficult portions to examine, is no less thorough than that accorded the more accessible body of the gland, the surgeon on occasions will fail in his quest to find a tumor which is actually present.

SUMMARY

1. A case is reported of adenoma of the islets of Langerhans, with symptomatic cure following removal of the tumor.

2. There are presented metabolic studies both before and after operation with additional information derived from the intravenous glucose and insulin tolerance tests.

3. Some evidence has been advanced to indicate that the insulin tolerance test may yet prove to be an aid of considerable importance in the diagnosis of hyperinsulinism and therefore of islet-cell pathology. We therefore make a plea for the further investigation of the possibilities of this test, as such, by its more frequent performance in cases of hypoglycemia.

REFERENCES

1. ÅKERBERG, E.: Hyperinsulinism and surgery, *Acta. Chir. Scand.*, 1939, lxxxiii, 104.
2. BANTING, F. G., and BEST, C. H.: Internal secretion of the pancreas, *Jr. Lab. and Clin. Med.*, 1922, vii, 251.
3. BERGONZI, M.: Basi anatomiche della ipoglicemia spontanea convulsivante: i tumori a cellule insulari del pancreas, *Riv. sper. di freniat.*, 1939, lxiii, 161.
4. CLARKE, J. M.: A brief review of functional hyperinsulinism, with report of a case showing improvement after partial pancreatectomy, *Austr. and New Zealand Jr. Surg.*, 1938, viii, 66.
5. COLLIP, J. B., and ANDERSON, E. M.: Studies on the thyrotropic hormone of the anterior pituitary, *Jr. Am. Med. Assoc.*, 1935, civ, 965.
6. DUNCAN, G. G., HAYWARD, G. W., and FLICK, J. B.: Hyperinsulinism: with report of two cases of adenoma of the islets of Langerhans, *Med. Clin. N. Am.*, 1939, xxiii, 1481.
7. FORBES, R. D., DAVIDSON, S. F., and DUNCAN, J.: Hyperinsulinism due to tumor of the pancreas, *West. Jr. Surg., Gynec. and Obst.*, 1939 (Feb.), xlvii, 76.
8. FRASER, R., MACLAY, W. S., and MANN, S. A.: Hyperinsulinism due to a pancreatic islet adenoma, *Quart. Jr. Med.*, 1938, xxxi, 115.
9. GRAY, P. A., and BURTNES, H. I.: Hypoglycemic headache, *Endocrinology*, 1935, xix, 549.
10. HARRIS, S.: Hyperinsulinism and dysinsulinism, *Jr. Am. Med. Assoc.*, 1924, lxxxiii, 729.
11. HERMANNSEN, J., and NESTMANN: Hyperinsulinismus und Pankreasadenom, *Klin. Wchnschr.*, 1938, xvii, 1589.
12. HOWLAND, G., CAMPBELL, W. R., MALBY, E. J., and ROBINSON, W. L.: Dysinsulinism. Convulsions and coma due to islet cell tumor of the pancreas, with operation and cure, *Jr. Am. Med. Assoc.*, 1929, xliii, 674.

13. JIRASEK, A., and POSTRANECKY, O.: Un cas d'adenome des ilots de Langerhans. Diagnostic—Operation—Guerison, *Presse Med.*, 1938, xlii, i, 672.
14. JONES, W. A., and MATTE, M. L.: Tumor of the pancreas, with hypoglycemia, *Med. Bull. Vet. Admin.*, 1938, xiv, 375.
15. KOEHLER, A. E., and HILL, ELSIE: Comparison of oral and intravenous glucose tolerance, *Proc. Am. Soc. Biol. Chem.*, 1938, xxxvii, 19.
16. KRAUSS, H.: Zur Klinik und Therapie des Pankreasadenomes, *Deutsch. Ztschr. f. Chir.*, 1939, ccli, 512.
17. LEVISON, L. A., and RAMSEY, T. L.: Spontaneous hypoglycemia associated with pancreatic adenoma: case report with operation and autopsy, *Ohio State Med. Jr.*, 1938, xxxiv, 869.
18. MALAMUD, N., and GROSH, L. C.: Hyperinsulinism and cerebral changes, *Arch. Int. Med.*, 1938, lxi, 579.
19. NICHOLSON, W. M., and HART, D.: Spontaneous hypoglycemia, *New Internat. Clin.*, 1938, ii, 251.
20. PARADE, G. W., and KINDLER, K.: Inselzellenadenom, durch Operation geheilt, *Klin. Wchnschr.*, 1938, xvii, 810.
21. WEST, H. F., and KAHN, M.: Adenoma of the pancreas with hyperinsulinism. Two proved cases, cousins, with surgical cure in one, *West. Jr. Surg., Gynec. and Obst.*, 1939, xlvii, 364.
22. WHIPPLE, A. O.: The surgical therapy of hyperinsulinism, *Jr. Internat. de Chir.*, 1938, iii, 1.
23. WHIPPLE, A. O., and FRANTZ, V. K.: Adenoma of islet cells with hyperinsulinism, *Ann. Surg.*, 1935, ci, 1299.
24. WILDER, R. M., ALLEN, F. N., POWER, M. H., and ROBERTSON, H. E.: Carcinoma of the islands of the pancreas, hyperinsulinism and hypoglycemia, *Jr. Am. Med. Assoc.*, 1927, lxxxix, 348.
25. WOMACK, N. A.: Hypoglycemia, *Surgery*, 1937, ii, 793.

EDITORIAL

MEDICAL NEWS FROM CHINA

THE following brief account of medical findings in a busy Red Cross Clinic in China has been contributed by one of the Fellows of the American College of Physicians who is at work at Soochow in the province of Kiangsu. It is a revealing report which will be read with interest by our membership.

"The Red Cross Clinics in Soochow have been in operation for 29 months. During this time 300,000 people, in round numbers, have been treated. Sixty per cent were from the city and the remaining 40 per cent were refugees from the surrounding city and country districts. Practically all were from the poorer classes. Soochow is located in the Yangste delta and the climate is considered temperate or subtropical.

"Some of the outstanding medical findings were:

"1. The prevalence and rapid rate of increase in tuberculosis since the beginning of the war. This is due to ignorance of the cause of the disease, over-crowding, lowered resistance and poor food. One out of every 10 medical patients has been diagnosed as suffering with tuberculosis in some form. Eighty per cent of the children under 12 show positive tuberculin tests.

"The methods used in the study of these cases have been: history, physical findings, sputum examination, sedimentation rate, tuberculin tests in children, and roentgenograms in a small percentage. In addition to the actual effort to treat the disease, a great deal of time has been spent in public health and educational work.

"2. Malnutrition and vitamin deficiency have been almost universal. The Chinese throughout the centuries have eaten polished rice, and have depended upon supplementary foods for vitamin B. Food costs have risen 400 per cent since the beginning of the war, and most of the foods rich in vitamin B have been dropped from the diet. Vitamin B deficiency has been present in 85 per cent of our patients. Beriberi, in its various forms, has been the most frequent clinical manifestation of this deficiency. With this B deficiency there is frequently associated nicotinic acid and riboflavin deficiency. Vincent's infection has been present in 40 per cent. Through the courtesy of Meade Johnson and Company, we were supplied with a large amount of nicotinic acid. It has been striking how rapidly the condition of the mouth, tongue and other mucous membranes improves under its use. The American and British Red Cross have supplied large quantities of wheat and vitamin B extracts. We have also used large amounts of sprouting beans and wheat as supplementary foods.

"Vitamin C deficiency has been diagnosed in 30 per cent of our patients, and vitamin A and D deficiencies in 40 per cent. The American Red Cross

and the Norwegian Consul in Shanghai have supplied us with several barrels of cod liver oil. This has been distributed largely to children.

"3. There have been three epidemics: measles, pertussis, and dengue fever. The last is supposed to have been introduced from Formosa by troop movements. Thousands have fallen victims. The acute onset, high fever, intense headache, leukopenia, and lymphocytosis have been outstanding features of the disease. Meningitis has been prevalent. It has responded to sulfapyridine. All of us have been impressed with the comparative infrequency of cholera. The Japanese have rigidly enforced vaccination and quarantine against this disease. Typhoid, paratyphoid and bacillary dysentery have been widespread. Preventive inoculations against the former have been extensively given.

"4. Malaria has taken a heavy toll. One out of four medical patients seen between June and November has had this disease. Tertian and quartan make up the larger percentage during the summer, and subtertian during the fall. Seventy-four per cent of the latter have shown liver damage, and 20 per cent albuminuria. We have been impressed with the absence of pernicious anemia, and the very low incidence of diabetes. Essential hypertension and rheumatic fever are also rare in China.

"5. Four thousand Kahn tests were done on selected cases. Twenty-three per cent were positive. Syphilis is rare in the country districts, but common in the port cities.

"6. Cirrhosis of the liver is frequent. Malaria, schistosomiasis and alcohol are the largest contributory factors.

"7. Intestinal parasites have been present in about the same proportion as during peace times. *Ascaris* has been present in 23 per cent, hookworm in 7 per cent, and *schistosoma* in 3 per cent.

"8. The lowly itch mite has caused almost as much discomfort as have machine gun bullets and shrapnel. On account of poverty, insufficient clothing, and poor bathing facilities, its presence is almost universal among the poor. Pustular infections and major surgical complications have frequently developed.

"9. We have been fortunate in having practically no typhus fever.

"10. It is impossible to measure with any yardstick the amount of nervous tension and mental conflict that has followed as the result of the war. This has been abundantly evident. On the whole, however, the people have been wonderfully philosophical and have stood their suffering bravely."

M. P. YOUNG, M.D., F.A.C.P.

REVIEWS

Bacteriology. By WILLIAM W. FORD, M.D., D.P.H., Emeritus Professor of Bacteriology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. 207 pages; 11 × 17 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, New York. 1939. Price, \$2.50.

This little volume is one of the handbooks in the "Clio Medica" series. In it is presented by periods the gradual accumulation of the knowledge that has affected the development of bacteriology. When necessary for clearness of presentation short biographies have been given of the important bacteriologists.

After a discussion of spontaneous generation, the earlier conceptions of the microbic theory of disease and the origin of suppuration, there is a chapter devoted to the growth of our knowledge of magnification. This is followed by a consideration of van Leeuwenhoek and his discovery of bacteria. Next are presented the contributions made to the solution of the various problems in the 18th and early 19th centuries. Three chapters are given to the work of Pasteur, Tyndall and Lister in the field of bacteriology; the rise of the German school of bacteriologists under Cohn; and the work of Koch. The development of immunology and serology is discussed in three chapters and the book closes with a presentation of the advances made during the first quarter of the 20th century and the trends in bacteriology. The author has presented in brief compass a clear picture of the development of our knowledge in this field. The book should be of value and interest to physicians, students and laymen. Its value is increased by the list of references to original sources.

F. W. H.

Modern Dermatology and Syphilology. By S. WILLIAM BECKER, M.D., and MAXIMILLIAN E. OBERMAYER, M.D. 871 pages, 461 illustrations; 19 × 26 cm. J. B. Lippincott Co., Philadelphia. 1940. Price, \$12.00.

A well illustrated textbook on dermatology and syphilology is a welcome addition to medical literature. The illustrations in this text are photographs, all of which are in good focus, and are well arranged. They are valuable adjuncts to the excellent clinical descriptions presented by the authors. The style of presentation is unusual in that each chapter is prefaced with a paragraph on orientation, which explains to the reader the reasons for the construction of that particular section. The chapters are presented in lecture style in a comprehensive manner, thus fulfilling the requisites of a good textbook.

An attempt has been made to classify the various skin diseases, and present them in the groups in which they belong, as for example: the coccogenous dermatoses, the seborrhea group, the atrophies, and others. This is very well done. The section on allergy in dermatology is well-written and instructive.

The chapters devoted to syphilotherapy do not follow any of the methods recommended by the Coöperative Clinical Group or the Public Health Service, but represent the opinions of the authors. The methods used are not orthodox, and are not to be recommended for general use by practitioners or students.

As a whole, this book may well be recommended as a suitable text on dermatology and syphilology.

H. M. R., Jr.

Problems of Nervous Anatomy. By J. BOEKE. VI plus 164 pages, with 48 illustrations; 14.5 × 23 cm. Oxford University Press, London: Humphrey Milford. 1940. Price, \$2.75.

This is a monograph comprised of three lectures given in England by invitation of the Universities of London and Oxford in 1938, together with an additional fourth lecture which gives further details of points discussed in the original lectures.

In the first chapter the author discusses changes in the spinal and sympathetic innervation of the skin during degeneration and regeneration. In this chapter he disagrees with the theory of Head that there exist two sets of nerve fibers supplying the skin receptors, the protopathic and epicritic fibers. The author contends that the protopathic sensation represents an early stage of nerve fiber regeneration and the acute discriminating epicritic sensation appears only after the nerve fibers are completely regenerated.

The second chapter deals with the sympathetic ground plexus which consists of a delicate network of nonmyelinated nerve fibers containing scattered nuclei. This plexus is described as being very rich in the different tissues of the body and brings every element of the body into connection with the sympathetic nervous system.

In the third chapter the author discusses the problem of the interstitial cells in this peripheral sympathetic network. He concludes that they are small nerve cells and further states that this terminal sympathetic nerve plexus is very primitive and from it the "larger cellular elements of the sympathetic system in the higher vertebrates have differentiated."

The neuron doctrine is discussed in the final chapter. He does not believe that the neuron should be considered as a unit anatomically set apart, as stated by Cajal. This he bases on the "physiological function of the sympathetic end formation and the interstitial elements in their syncytial arrangement."

The book is well illustrated. The limited scope and unsettled state of the subject make it of interest principally to neuro-anatomists, physiologists, and possibly neurologists.

E. F. C.

COLLEGE NEWS NOTES

NEW LIFE MEMBER

Dr. Jerome E. Cook, F.A.C.P., St. Louis, Mo., became a Life Member of the American College of Physicians on February 25, 1941.

GIFTS TO THE COLLEGE LIBRARY

The following gifts of reprints to the College Library of Publications by Members are gratefully acknowledged:

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Dr. Morris L. Drazin (Associate), Jackson Heights, N. Y.—1 reprint;
Dr. Norbert Enzer, F.A.C.P., Milwaukee, Wis.—1 reprint;
Dr. Irving Greenfield (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—1 reprint;
Dr. J. Fletcher Hanson, F.A.C.P., Macon, Ga.—3 reprints;
Dr. Frank B. Marsh (Associate), Salisbury, N. C.—3 reprints;
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—4 reprints;
Dr. Frederick Tice, F.A.C.P., Chicago, Ill.—1 reprint;
Lieut. Hugh G. Whitehead (Associate), (M. C.), U. S. Navy—4 reprints.

AMERICAN BOARD OF INTERNAL MEDICINE RECOGNIZES SUB-SPECIALTIES

At the February meetings of the Advisory Board for Medical Specialists and of the Council on Medical Education and Hospitals of the American Medical Association, the proposal of the American Board of Internal Medicine for the recognition of the following sub-specialties was approved: Allergy, Cardiovascular Diseases, Gastroenterology and Tuberculosis.

The mechanism for obtaining certification in the above listed sub-specialties of internal medicine has been outlined as follows:

1. All candidates must pass the same written examination in internal medicine.
 2. Candidates successful in the written examination are eligible for the practical examination given before the meeting of the American Medical Association and the American College of Physicians each year.
 - a. The examination upon the long case will be conducted by a team led by a member of the American Board of Internal Medicine.
 - b. The examination upon the short case will be conducted by a team composed of a member of the American Board of Internal Medicine and an examiner in the sub-specialty selected from a list submitted by the Advisory Committee of the interested sub-specialty.
 - c. Upon the successful conclusion of this portion of the practical examination, the candidate will be turned over to the sub-specialty representative for an examination in such special technics as may apply to the particular field.
- The Advisory Committees coöperating in this effort are:

Allergy

Dr. J. Alexander Clarke, Jr.
 Dr. Robert A. Cooke
 Dr. Leslie Gay
 Dr. Richard A. Kern
 Dr. George Piness
 Dr. Francis M. Rackemann

Cardiovascular Diseases

Dr. Harold M. Marvin
 Dr. William D. Stroud
 Dr. Irving S. Wright

Gastro-enterology

Dr. Albert F. R. Andersen
 Dr. Henry L. Bockus
 Dr. George B. Eusterman

Tuberculosis

Dr. J. Burns Amberson, Jr.
 Dr. Paul P. McCain
 Dr. Lewis J. Moorman

Candidates eligible for all practical examinations of the American Board of Internal Medicine in the future will be circularized in this matter prior to the examination. An additional fee of ten dollars is required for the sub-specialty examination.

 WESTERN PENNSYLVANIA REGIONAL MEETING OF COLLEGE MEMBERS

Under the Governorship of Dr. R. R. Snowden, a Regional Meeting of Fellows and Associates of the College was held at Pittsburgh, March 5, 1941. Meetings and dinner were held at the Pittsburgh Athletic Club opposite the temple of learning of the University of Pittsburgh. The afternoon program consisted of an informal presentation of certain research activities at present being conducted in the laboratories of the University of Pittsburgh School of Medicine, as follows:

1. The Quantitative Determination of Female Hormones. Donald A. Wilson, Ph.D.
2. Whole Blood and Plasma Banks. Mortimer Cohen, M.D., F.A.C.P.
3. Demonstration of Measurement of Radio Activity by the Geiger Counter. Elmer Hutchisson, Ph.D.
4. Experimental Studies on Prenatal Development. Davenport Hooker, Ph.D., Sc.D.
5. Experimental Hypertension in Dogs. J. M. Rogoff, M.D., Sc.D.

There was a social hour from 5:30 to 6:30 followed by dinner at 7 o'clock. Dr. Clement R. Jones, F.A.C.P., for many years Treasurer of the College, was Toastmaster. Dr. Edward L. Bortz, F.A.C.P., Philadelphia, brought greetings from the Eastern Pennsylvania members, for which he is the Governor. Mr. Edward R. Loveland, Executive Secretary of the College, gave an address entitled "The Growth and Activities of the College," reviewing in particular the growth and activities of the College during the last fifteen years, the period for which he has been the Executive Secretary. Dr. George Morris Piersol, F.A.C.P., Philadelphia, Secretary General of the College, gave an address on "Criteria and Standards of Admission."

A Bulletin of the Chicago Municipal Tuberculosis Sanitarium, devoted to Tuberculin Testing in the Chicago Schools, by Dr. Frederick Tice, F.A.C.P., President of the Board of Directors of the Sanitarium, has been issued recently and dedicated to the memory of Dr. Allan Joseph Hruby, F.A.C.P., the late Secretary of the Board of Directors, who died late in 1939. Also, recently, a bronze memorial plaque was unveiled at the Sanitarium and dedicated to Dr. Hruby.

The Annual New Orleans Graduate Medical Assembly was held at Hotel Roosevelt, March 3-6, with clinics conducted at various hospitals on March 7. Among the speakers were: Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, "Pancreatitis"; Dr.

Charles F. McKhann, F.A.C.P., Ann Arbor, "Progress in the Control of Respiratory Disease"; Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn., "The Eczemas"; Dr. Paul D. White, F.A.C.P., Boston, "The Range of the Normal Heart"; Dr. Ernest E. Irons, F.A.C.P., Chicago, "Aspiration Pneumonia."

The Bergen County, New Jersey, Medical Society arranged a special program on Hypertension at Hackensack, January 14. Dr. Soma Weiss, F.A.C.P., of Boston, gave the chief address and this was followed by a panel discussion presented by Dr. Benjamin I. Ashe, F.A.C.P., Dr. Arthur C. DeGraff, F.A.C.P., Dr. Asa L. Lincoln, F.A.C.P., and Dr. Irving S. Wright, F.A.C.P., all of New York City.

The Harvard Medical School, Boston, opened a course of weekly free public lectures on medical subjects, beginning January 5. Dr. William B. Breed, F.A.C.P., gave a lecture on "The Common Cold and How to Treat It," and Dr. Reginald Fitz, F.A.C.P., gave a lecture on "The Pathway of Medical Discovery."

The Board of Doctors Hospital of Philadelphia has authorized the establishment of the Burge Tuberculosis Clinic, in honor of Dr. Frank Walton Burge, F.A.C.P., Philadelphia, Pa.

Dr. Reginald Fitz, F.A.C.P., Boston, Mass., has recently become President of the Boston School of Occupational Therapy.

Dr. George Herrmann, F.A.C.P., Galveston, was elected President of the Texas Club of Internists, Dr. Edgar McPeak, F.A.C.P., San Antonio, Vice-President, and Dr. Merritt B. Whitten (Associate), Dallas, Secretary-Treasurer, at their recent meeting.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Newer Concepts in the Treatment of Diabetes" before the members of the Cumberland County Medical Society in Bridgeton, N. J., February 11, 1941.

On February 20, Dr. August W. F. Westhoff, F.A.C.P., Richmond Hill, N. Y., was honored at a dinner given in commemoration of the completion of fifty years in the practice of medicine.

Dr. Harold J. Harris (Associate), Westport, N. Y., spoke on "Brucellosis (Undulant Fever)—Clinical and Subclinical" at the meeting of the Worcester District Medical Society, Worcester, Mass., April 9, 1941.

The Sixth Annual Postgraduate Institute of the Philadelphia County Medical Society was held in Philadelphia, Pa., March 31–April 4, 1941. The topic of this Institute was "Symposia on Modern Therapy," and the following Philadelphia members of the College participated:

- Dr. Samuel Goldberg, F.A.C.P., "Management of Pyuria in Childhood";
- Dr. Thomas A. Johnson, F.A.C.P., "Control of the Constitutional Factors of Uncomplicated Peptic Ulcer";
- Dr. Martin E. Rehfuss, F.A.C.P., "Dietary and Medicinal Management of Uncomplicated Peptic Ulcer";
- Dr. T. Grier Miller, F.A.C.P., "Medical Management of Bleeding Peptic Ulcer";

- Dr. Harrison F. Flippin, F.A.C.P., "The Pharmacology and Toxicology of Sulfanilamide and Its Derivatives";
- Dr. Charles C. Wolferth, F.A.C.P., "Treatment of Cardiovascular Syphilis";
- Dr. W. Osler Abbott, F.A.C.P., "Diagnosis and Medical Management of Apparent Pyloric Obstruction";
- Dr. William A. Swalm, F.A.C.P., "Medical Management of Chronic Gall-bladder Disease";
- Dr. Henry L. Bockus, F.A.C.P., "Differential Diagnosis of Jaundice";
- Dr. Henry J. Tumen (Associate), "Treatment of Hepatocellular Type of Jaundice";
- Dr. George E. Pfahler, F.A.C.P., "Radiological Treatment of Cancer of the Uterus";
- Dr. Richard A. Kern, F.A.C.P., "Modern Treatment of Asthma";
- Dr. Edward L. Bortz, F.A.C.P., "Geriatrics—New Light on Old Folks";
- Dr. Edward Rose, F.A.C.P., "Therapy of Hypothyroid and Para-thyroid Diseases";
- Dr. Russell S. Boles, F.A.C.P., "Management of So-called Irritable Colon and Constipation";
- Dr. Edward A. Strecker, F.A.C.P., "The Value of Psychoanalysis as Related to the Needs of the General Practitioner";
- Dr. Kendall A. Elsom (Associate), "Treatment of Small Intestinal Disturbances by Drugs";
- Dr. Charles L. Brown, F.A.C.P., "Recent Advances in the Treatment of Pneumonia";
- Dr. Henry K. Mohler, F.A.C.P., "The Use and Abuse of Sedatives and the Barbiturates";
- Dr. Sigmund S. Greenbaum, F.A.C.P., "Treatment of Acute and Chronic Urticaria";
- Dr. W. Edward Chamberlain, F.A.C.P., "The Radiological Management of Hodgkin's Disease, Lymphosarcoma and Leukemia";
- Dr. George Morris Piersol, F.A.C.P., "Gastric Neurosis";
- Dr. Louis H. Clerf, F.A.C.P., "Treatment of Tumors of Larynx and Hypopharynx";
- Dr. William D. Stroud, F.A.C.P., "Treatment of Rheumatic Heart Disease";
- Dr. John H. Willard, F.A.C.P., "Management of Colonic Diverticulosis and Diverticulitis";
- Dr. Charles W. Dunn, F.A.C.P., "The Field of Male Hormone Therapy in General Medicine."

The Northern Medical Association of Philadelphia held its 95th Annual Dinner March 17, 1941, in Philadelphia, Pa. Dr. Edward J. G. Beardsley, F.A.C.P., Professor of Clinical Medicine at Jefferson Medical College of Philadelphia, was one of the guests of honor.

The Colorado State Medical Society conducted its 9th Annual Midwinter Postgraduate Clinics, February 5-7, 1941, in Denver, Colo. Among those who participated were:

- Dr. Ralph Bowen, F.A.C.P., Houston, Tex.—"The Practical Management of the Asthmatic Child";
- Dr. Thomas D. Cunningham, F.A.C.P., Denver, Colo.—"Borderline Allergies";
- Dr. William S. Middleton, F.A.C.P., Madison, Wis.—"Bronchiogenic Carcinoma: A Challenge in Diagnosis and Treatment."

Dr. John H. Musser, F.A.C.P., New Orleans, La., has been named State Health Director of Louisiana and Dr. Joseph E. Knighton, F.A.C.P., Shreveport, La., Vice-Chairman of the Louisiana State Board of Health.

Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Pa., has been appointed Editor of the *Pennsylvania Medical Journal*.

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., has received a government travel grant to visit South America, under the provisions of the Second Deficiency Appropriation Act of 1940. This act provided funds for the exchange of distinguished cultural, professional and artistic leaders between the United States and the other American republics.

The Department of Medicine of the New York Post-Graduate Medical School will conduct a new course entitled, "Recent Advances in Tropical Medicine," May 19-23, 1941, under the direction of Dr. Zacharias Bercovitz, F.A.C.P., New York, N. Y. The purpose of this course is to bring to physicians a review of the fundamentals of the various subjects in tropical medicine, and the more recent advances that have come from research. To this end, arrangements have been made to have authorities in their respective fields give lectures and demonstrations in their specialties. Clinical and laboratory material is available for study and demonstration, and the students are given an opportunity for practical work in clinical parasitology. The following members of the College will give lectures and demonstrations:

- Dr. Thomas T. Mackie, F.A.C.P., "Amebic Dysentery: Pathology, Symptoms and Treatment" and "Deficiency Diseases";
- Dr. Zacharias Bercovitz, F.A.C.P., "Amebic Dysentery: Differential Diagnosis with Special Reference to Cellular Exudates and Complications of Amebiasis and Their Treatment," "Amebic Dysentery: Demonstration of Diagnostic Methods," "Bacillary Dysentery: Diagnosis and Treatment," and "Trichinosis";
- Dr. Claude E. Forkner, F.A.C.P., "Kala Azar";
- Dr. Elliston Farrell (Associate), "Leptospirosis" and "Relapsing Fever and Rat Bite Fever";
- Dr. Arthur W. Grace, F.A.C.P., "Lymphogranuloma Venereum."

OBITUARIES

SIR FREDERICK BANTING, K.B.E.

It was with profound regret that, not only the people of Canada, but people of all lands, learned of the untimely death of Sir Frederick Banting, F.A.C.P., Toronto, Ont., Canada, in an aeroplane accident, off the coast of Newfoundland, while flying to England on February 21st last.

Following his brilliant work in 1922 leading to the discovery of Insulin in association with Dr. Charles H. Best and Dr. J. R. McLeod, universities and scientific societies the world over have given him recognition, and provision had been made by the Dominion Government to enable him to pursue an uninterrupted program of research.

For many years he has been Professor of Medical Research at the Banting Institute, University of Toronto, and has been actively engaged in many problems of medical research, some of which are also recognized as of great scientific value.

Prior to the outbreak of war, Sir Frederick, as Chairman of the National Research Council's Associate Committee on Medical Research, turned his attention to research in the field of military medicine, and already valuable work had been accomplished. In fact, this flight to England, it is believed, had to do with important research work in aviation, while prior to this he had already taken part in work which had led to improved methods of storing blood for use later in transfusions, thus making possible the present campaign of the Red Cross to provide large scale blood banks, for Canadian and British troops and civilians.

In 1938 Sir Frederick received recognition for work on cancer, and late that year, the director of the Imperial Cancer Research Fund in London acclaimed the findings of Dr. Banting as "substantial contributions to the problem."

For Dr. Banting's work, in the discovery of Insulin, he was granted the Nobel Prize in 1923, and illustrating the character of the man is the fact that when the Nobel Prize Committee had not given equal recognition to Dr. Best, he shared with that scientist his own half of the prize.

Dr. Banting did not go to Stockholm to receive the Nobel Prize until 1925, when he was asked to deliver the Nobel Lecture. He was the first Canadian honored by such an invitation.

In 1927 he was asked to investigate the feasibility of establishing in the Canadian Arctic, hospitals and other facilities for giving medical care to the Eskimo. He went north for three months aboard the Dominion Government steamship *Beothic*. In his report he found it would not be feasible to establish hospitals because of the Eskimo's roving life.

During his trip to the north the doctor had time to indulge his favorite hobby, painting, and he came home with numerous pictures of Arctic scenes which attracted wide notice.

In recognition of his services to medicine and humanity he was made a life member of the Canadian Clubs of Toronto, New York and London; while in the King's Birthday Honours, published on June 4, 1934, Knighthood was bestowed upon him.

He was elected to Fellowship in The American College of Physicians in 1923.

At the outbreak of the war Sir Frederick enlisted for active service, and at the time of his death was a Major in the Canadian Army.

Sir Frederick has a long list of achievements to his credit, but, quite as important, is the influence which he has exerted upon the young medical men of Canada, for his chief interest in medicine was as a research student and as such he has implanted his influence upon a large group of followers who will consider it their great privilege to continue the work that he has commenced.

Sir Frederick was buried with full military honours on Tuesday, March 4, 1941, the service being held in Convocation Hall, University of Toronto, the Hall in which he received his first degree in medicine in 1917.

Frederick Grant Banting was born in Alliston, Ontario, in 1891, and is listed as follows: M.B., University of Toronto, Faculty of Medicine 1917; M.D., 1922; Sc.D.; LL.D.; L.R.C.P.; F.A.C.P.; M.R.C.S.; F.R.C.S.; London, 1930; F.R.C.S., Canada, 1931; F.R.S., London, 1935; Knight Commander of Civil Division, Order of British Empire, 1934—Sir Frederick Banting, K.B.E.; Professor of Medical Research, Banting Institute, University of Toronto, Faculty of Medicine.

J. H. HOLBROOK, M.D., F.A.C.P.,
Governor for Province of Ontario.

DR. ALBERT BENJAMIN McCREARY

The people of Florida, and particularly the medical profession, have sustained a great loss in the passing of Dr. Albert Benjamin McCreary (Associate), Jacksonville, State Health Officer for the State of Florida. Dr. McCreary achieved a remarkable record during his brief term of office of a year and a half. From the time of his appointment to his death, he awakened the public conscience of Florida to the advantages of public health, with the result that never before in the history of the state has there been such wide-spread interest in the health of the public.

Dr. McCreary worked tirelessly and without thought of himself in his zeal to serve the people of Florida to the best of his ability. When the American Public Health Association made their now widely read survey, "The Health Situation in Florida," Dr. McCreary accepted this as the foundation for a program which was designated to eventually bring the administration of public health in Florida to the very highest possible standard.

The program was an ambitious one that obviously would consume much time to complete and no one was as aware of the arduous task ahead as Dr.

McCreary. Although he was not destined to live to see it completed, at least he had the satisfaction of being the moving force in getting it under way.

Dr. McCreary was always the first to refuse credit for himself and give it to his co-workers. He had the enviable faculty for inspiring those associated with him to put their very best effort into their work.

Of all the honors which came to Dr. McCreary during his lifetime—and there were many—none was so great as the loyalty of his staff and the enthusiasm with which private physicians throughout the State supported him in his undertakings.

Dr. McCreary died in a Jacksonville hospital on the evening of January 24, at the age of 45. Besides his widow, Mrs. Cornelia Varnell McCreary, he leaves two daughters, Madge and Cornelia, and two sons, Albert and Lloyd; his mother, Mrs. Mamie Smith McCreary, New York City; a sister, Mrs. W. A. Radspinner, also of New York City.

Dr. McCreary was the son of the late Dr. L. B. McCreary, of Kingsport, Tenn.

Dr. McCreary was appointed August 4, 1939, by Governor Fred P. Cone to succeed the late Dr. W. A. McPhaul. For four years prior to his appointment as State Health Officer, he directed the work of the Bureau of Local Health Service of the Florida State Board of Health.

Dr. McCreary was well known throughout the South in both medical and public health circles. Among the positions he held during the past 17 years were epidemiologist, Department of Health, Memphis; assistant in public health, University of Tennessee, Memphis; member of the staff, General Hospital and Saint Joseph's Hospital, Memphis; director, bureau of epidemiology, North Carolina State Board of Health; health officer, Northampton County, Virginia, and also of Richmond County, North Carolina; member of the staff, State Hospital, Raleigh, N. C. His A.B. degree was earned at King College, Bristol, Tenn.; his M.D. at University of Tennessee, Memphis.

He was immediate past president of the Florida Public Health Association and member of the National Malaria Committee. He was an Associate of the American College of Physicians, and held membership in the Duval County Medical Society, the Florida Medical Association, American Medical Association and the American Public Health Association. Dr. McCreary was a member of the Morocco Temple and the Jacksonville Rotary Club.

At the Florida Public Health Association convention in Tampa last December, the Cuban government conferred upon Dr. McCreary the honor of Commander of the Order of Carlos Finley in recognition of his contribution to the advancement of public health. The order was conferred personally by Dr. Felix Hurtado, associate secretary of health of Cuba.

A. J. LOGIE, M.D., F.A.C.P.,
Jacksonville, Fla.

DR. CLINTON DURHAM FIFE

Dr. Clinton Durham Fife, Fellow, Dayton, Ohio, died October 24, 1940. He was born at Wilmington, Ohio, May 23, 1895, and received his degree of Bachelor of Science from Hiram College in 1918, and his degree of Doctor of Medicine from Western Reserve University of Medicine in 1921. For many years he had been a member of the medical staff and an instructor to nurses of the Miami Valley Hospital. He was a member of the senior medical staff of the Good Samaritan Hospital. He was a member of the Montgomery County Medical Society, Ohio State Medical Society, American Medical Association, a diplomate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians since 1931.

DR. ALBERT A. GETMAN

Dr. Albert A. Getman, Fellow, Syracuse, N. Y., died October 28, 1940. He was born in Richfield Springs, N. Y., in 1888, attended Hamilton College at Clinton, N. Y., and received his medical degree from the New York Homeopathic Medical College in 1915. From 1919 to 1921, he was Assistant Attending Physician, and from 1921 to 1922, Attending Physician at the Syracuse Homeopathic Hospital. Since 1922, Dr. Getman had been Attending Physician at the Syracuse General Hospital. He was a member of the Syracuse Academy of Medicine, the Medical Society of the State of New York and the American Institute of Homeopathy. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1926 (a Life Member since 1930).

ABSTRACT OF MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

DECEMBER 15, 1940

The regular autumn meeting of the Board of Regents was held at the College Headquarters, Philadelphia, December 15, 1940, at 10:00 a.m.; President James D. Bruce presided, Mr. E. R. Loveland acted as Secretary and the following were present:

James D. Bruce*President*
Roger I. Lee*President-Elect*
Robert A. Cooke*First Vice-President*
Henry M. Thomas, Jr.*Third Vice-President*
William D. Stroud*Treasurer*
George Morris Piersol*Secretary-General*
T. Homer Coffen
Ernest E. Irons
D. Sclater Lewis
Hugh J. Morgan
James E. Paullin
Francis G. Blake
Reginald Fitz
David P. Barr
J. Morrison Hutcheson
Walter W. Palmer
O. H. Perry Pepper
Gerald B. Webb
Maurice C. Pincoffs
Charles H. Cocke

Guests to this meeting included Dr. Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses; Dr. William Gerry Morgan, Historian; Dr. James Alex. Miller, Chairman of the Committee on Survey and Future Policy, and Dr. William B. Breed, General Chairman of the Twenty-fifth Annual Session.

The Secretary read abstracted Minutes of the three meetings of the Board of Regents held at Cleveland, April, 1940, which were approved as read.

The Secretary also read communications from absent members, expressing their regret at not being present (Dr. Charles T. Stone, Dr. Egerton L. Crispin, Dr. James G. Carr and Dr. William J. Kerr). Dr. Kerr also extended an invitation for the College to meet in San Francisco in 1942.

The following communications were presented:

- (1) American Red Cross, expressing thanks for free advertising space for an announcement in the ANNALS OF INTERNAL MEDICINE;
- (2) National Research Council, Committee on Medicine, thanking the College for helpfulness in preparing a card list of all members of the College, to be used in the classification of physicians;

- (3) Cook County Hospital requesting contributions for a plaque to be erected in memory of the late Dr. Bernard Fantus, F.A.C.P., for whom its new outpatient clinic has been named;
- (4) Cleveland Medical Library Association, expressing thanks to the College for furnishing a replica of the John Phillips Memorial Medal for its Museum;
- (5) Dr. Maximilian A. Ramirez, F.A.C.P., New York, N. Y., concerning minimum standards for hospitals;
- (6) Dr. William H. Walsh, F.A.C.P., Chicago, suggesting a Committee on Hospitalization to be established in connection with medical preparedness program;
- (7) Dr. John W. Hansen, Milwaukee, reading as follows:

"I suggest substituting the term 'Political Medicine' for the terms 'Federal,' 'State' or 'Socialized Medicine' henceforth in all medical papers, speeches and all publicity pertaining in any way to this subject. It will throw the issue squarely into the laps of the politicians where it belongs and where it originated. It may not prove so easy for politicians to explain to the public just why it should be necessary to force politics between the 'Patient and his Physician.' Also, the use of the term 'Political Medicine' is a clear and simple explanation to those persons who are 'in the dark' as to the true meaning of 'Socialized Medicine.'"

Dr. James E. Paullin, Chairman, presented the report of the Committee on Public Relations. Among problems presented and remedies recommended were: (1) The fitness of a physician to teach medicine should be referred to the Council on Medical Education and Hospitals of the American Medical Association; (2) The matter of obtaining patents by universities and foundations should be referred to the American Medical Association, since that body has a committee studying the problem; (3) The claim of special cures for any disease, when submitted to the College for opinion, must be accompanied by sufficient scientific data; (4) The appointment of a committee on hospitalization to work in collaboration with others interested in hospital affairs as administrators is not a particular problem of the College, but should be considered by the American Hospital Association; (5) The program and policies of the Interne Council of America were examined, and it was recommended that this problem be referred to the Council on Medical Education and Hospitals of the American Medical Association for its study; (6) The receipt of the Rockefeller Foundation's International Health Division's 1939 annual report was acknowledged with thanks; (7) A member's complaint concerning rebates given to physicians by laboratories in consideration of work sent to them was acknowledged, and it was recommended that since the American College of Physicians is in sympathy and agreement with the rules and ethics as outlined by the American Medical Association, the complaint should be filed with the member's local medical society. The practices outlined, in the opinion of the Committee, violate the code of ethics of all physicians.

By resolution, the Board of Regents approved of these recommendations individually and as a whole. Also upon recommendation of the Committee on Public Relations, by resolution adopted by the Board of Regents, the resignations of Dr. Gerald R. Fisher of Colorado Springs, and of Dr. Carlos E. Munoz MacCormick of Santurce, P. R., were accepted; likewise, the annual dues of a Fellow were waived for 1940 and thereafter as long as he may be incapacitated for the practice of medicine. The Chairman of the Committee on Public Relations was directed to address a letter to a Fellow of the College, explaining the duties of a territorial College Governor, and explaining that there is no established custom requiring applicants for Associateship to be interviewed by all members of the organization in his locality.

A report followed by Dr. Paullin, Chairman of an advisory committee to the armed services of the United States appointed by President Bruce, consisting of Dr. Roger I. Lee, Dr. Ernest E. Irons, Dr. Edward L. Bortz and Dr. J. E. Paullin. "This

committee has been quite active in its coöperative efforts with the Medical Preparedness Committee of the American Medical Association, with the Committee on Medicine of the National Research Council, and, through these committees, with the Surgeons General of the U. S. Army, U. S. Navy and U. S. Public Health Service. . . . At the present time, through the Committee on Medicine of the National Research Council, a request has been made that an evaluation be made of those physicians in the United States who have listed themselves as practitioners of Internal Medicine. Such information can be most valuable in helping corps area surgeons to obtain adequate, well-trained personnel for hospitals located in camps, cantonments and general hospitals. It was requested that the Committee on Public Relations of this College endorse the efforts of the Advisory Committee to the National Services and it was moved by President Bruce, seconded by Dr. Webb, and carried, that the report as presented by Chairman Paullin to the Committee on Public Relations be presented to the Board of Regents at its annual session, and that the Committee on Public Relations endorse the work of the liaison committee, and it recommends to the Board of Regents that the American College of Physicians assume responsibility for helping in the organization and preparation of data which will be useful for the Armed Forces."

On motion by Dr. Paullin, seconded and regularly carried, the above report was adopted.

Dr. William Gerry Morgan, College Historian, presented the completed book on the "History of the American College of Physicians—Its First Quarter Century." He expressed the hope that the History will prove of some interest to members and of permanent value to the College. Copies of the completed History were distributed to each member of the Board of Regents, and on motion by Dr. Roger I. Lee, seconded by Dr. James E. Paullin, and unanimously carried, it was

RESOLVED, that the Board of Regents accept the report of the Historian with gratitude.

The Secretary, Mr. Loveland, called to the attention of the Board that the original resolution for the distribution of the History provided merely that a copy be distributed to all Masters and Fellows of the College free of charge. No provision was specifically made for distribution of the History to Associates or to those Associates who shall advance to Fellowship during the current year, or during years to come. 3,500 copies of the History were ordered, but an additional 500 copies were run off on flat sheets without being sent to the bindery, held as a possible safeguard against an exhausted supply, to be bound when needed.

Upon motion by Dr. James E. Paullin, seconded and carried, the matter of furnishing copies of the History to Associates or to all men advanced to Fellowship within the next few years, as well as the binding of the additional copies, was referred to the Committee on Survey and Future Policy for later report at the current meeting.

The Secretary-General, Dr. George Morris Piersol, reported the deaths of 33 Fellows and five Associates (total, 38), and the addition of six Life Members since the preceding meeting of the Board of Regents.

As Chairman of the Committee on Credentials, Dr. Piersol proceeded with the report of that Committee. The Committee on Credentials had spent the preceding day, December 14, examining the credentials of candidates, an analysis of the number and recommendations of the Committee being as follows:

Candidates for FELLOWSHIP:

Recommended for Advancement to Fellowship:

As of December 15, 1940	115
As of April 20, 1941	19 134

Recommended for Direct Election to Fellowship	10
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TOTAL, Recommended Elections to Fellowship	144
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Recommended for Election First to Associateship	6
Deferred for Further Investigation or Adequate Material	18
Rejected (Proposals to be Withdrawn)	12
	<hr/> 180

Candidates for ASSOCIATESHIP:

Recommended for Election	138
Fellowship Candidates Recommended for Election to Associateship First	6
	<hr/>
TOTAL, Recommended Elections to Associateship	144
Deferred for Further Investigation or Other Credentials	9
Rejected (Proposals to be Withdrawn)	28
	<hr/> 181

On motion by Dr. Piersol, seconded and regularly carried, it was

RESOLVED, that the following list of 125 candidates shall be and are herewith elected to Fellowship in the American College of Physicians. (This list was published in the January, 1941, issue of this journal.)

On motion by Dr. Piersol, seconded and regularly carried, it was

RESOLVED, that the following list of 19 candidates, having met the requirements for Fellowship in every regard, with the exception that their three-year minimum term will not expire until April 20, 1941, shall be elected Fellows "As of April 20, 1941." (This list was published in the January, 1941, issue of this journal.)

On motion by Dr. Piersol, seconded and regularly carried, the following list of 144 candidates shall be and are herewith elected Associates of the American College of Physicians. (This list was published in the January, 1941, issue of this journal.)

On the recommendation of the Committee on Credentials and in accordance with provisions of the By-Laws, three Associates were dropped from the Roster for failure to meet the requirements for Fellowship in the maximum five-year Associate term.

Dr. Piersol then presented the following analysis of Associate Classes from 1929 to 1935, showing the degree to which Associates had met the requirements for Fellowship within the maximum five-year term prescribed in the By-Laws:

ANALYSIS OF ASSOCIATE CLASSES FROM 1929 TO 1935

(Beginning 1929, the By-Laws specified that Associates thereafter elected must qualify for Fellowship within a maximum five-year period, or be automatically dropped from the Roster.)

Date	Associates Elected	Dropped	Resigned	Deceased	Qualified for Fellowship	Percentage Qualified
1929	54	12	1	0	41	76%
1930	67	18	5	0	44	65.6%
1931	102	18	4	2	78	76.5%
1932	86	10	3	3	70	81.4%
1933						
Feb.	112	10	5	0	97	86.6%
Dec.	92	11	1	0	80	87%
1934						
Apr.	96	16	1	0	79	82.3%
Dec.	93	7	0	2	84	90.3%
1935						
Apr.	151	18	4	2	127	84.1%
Dec.	96	4	3	0	89	92.7%

By motion, seconded and regularly carried, one Associate was dropped from the Roster for failure to take up election within the period of one year as prescribed by the Board of Regents.

Dr. Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, reported a continuation of the work that had been begun and carried out by Dr. Hugh J. Morgan and Dr. Henry M. Thomas, Jr., of the original Committee on Postgraduate Education. Dr. Bortz and his Committee had collected during the past year a large amount of data by distributing a questionnaire to members of the College and by obtaining information from the directors of courses given in previous years and special reports from members of the College who had pursued courses in previous years. Universal enthusiasm was manifested by student-physicians who had taken the courses previously, there being but one criticism, namely, that in some courses there had been too many didactic lectures, whereas the registrants preferred more practical instruction. The general tenor of the reports was that the courses should be limited to fewer students and have a more intimate contact with the teachers. Several members indicated that they would like to take one or more courses in the future. After the data had been collected, the Committee communicated with each member of the Board of Regents and each Officer, asking for frank expressions of opinion about the further development of postgraduate instruction under the auspices of the College. Of some 4,000 questionnaires sent out, 918 were returned and 593 members expressed a desire to attend the courses in 1941. Of these, 282 gave a positive and definite indication of taking courses in 1941, and the balance expressed the desire to attend if at all possible. Dr. Bortz pointed out that the Postgraduate Courses were initiated by the College in 1938 when 117 men registered; in 1939 there were 118, and in 1940, 130. A marked increase in interest was manifested for 1941. There had been noted an increasing activity in the interest on the part of institutions, colleges, medical schools and clinics in their desire to become affiliated with the American College of Physicians in giving these courses. Some institutions that previously were unwilling to offer courses had during the current year, without approach on the part of the College, expressed a desire to offer their facilities, personnel and equipment in coöperating with the College. Dr. Bortz said there could be no doubt that more and more the medical profession of this country is looking to the College for leadership in the field of graduate study in Internal Medicine, and that more and more this is becoming an important activity of the College.

Dr. Bortz summarized the interest of those members who returned the postgraduate questionnaire, partially, as follows: cardiology, 332; gastro-enterology, 136; allergy, 67; diseases of the chest, 51; blood diseases, 47; neurology, 33; arthritis and rheumatism, 25; pediatrics, 20. Only a limited few indicated interest in the field of military medicine. With an increasing appreciation of the national situation, Dr. Bortz thought that more men would be interested in a course in military medicine. He said Dr. Pepper had particularly recommended that such a course be established, because of the large number of physicians who would be directly or indirectly involved in military medicine in the immediate future. There could be established another course bearing on military medicine, such as tropical medicine, chemotherapy, infectious diseases, sanitation and venereal diseases and such similar interesting subjects. The Committee on Postgraduate Courses had been guided entirely by the expressed interests of the members of the College as exemplified in the returned questionnaires. Due to Dr. Pepper's pertinent suggestion, the Committee, after discussing the matter carefully, had approached Dr. Wallace M. Yater, of Washington, asking him to make a survey of the availability of such a course under the Public Services of the United States at the Walter Reed General Hospital. Needless to say, all of the men on the staff of the Walter Reed General Hospital and connected with the military services are exceedingly busy, but realizing the value of such a course to the men anticipating

military service, they readily agreed to organize a course, which was incorporated in the College program for 1941.

Dr. Bortz brought up the matter of the relationship between medical schools where courses may be given and the American College of Physicians sponsoring the courses. The Committee had proceeded with the feeling that it should appoint directors of courses and the directors should arrange their courses in conference with and with the approval of the medical schools or hospitals at which the courses shall be given. Dr. Bortz presented the roster of postgraduate courses for 1941, including three February courses and seven pre-meeting courses, and then referred to numerous helpful recommendations made by Officers or members of the Board of Regents, and suggested that many were of such importance that they should deserve special study by an authorized committee. He referred particularly to a recommendation from Dr. Pincoffs that the College establish clinical fellowships, it being infinitely more valuable for the American College of Physicians to interest itself in the development of clinical training rather than concentrate on one or two research men. Another important and pertinent suggestion received, that since the College is growing and there is this increasing interest in the field of further training in advanced medicine, that the country be divided geographically into several areas or regencies, with a Regent at the head of each and a committee of Governors acting under the local Regent to study the needs in that particular locality, with particular reference to further study in Internal Medicine and other problems pertinent to that particular territory.

Dr. Bortz distributed to the Regents a map showing a possible division of the country into regencies, giving a distribution of the members in each regency, the Governors, medical schools, etc. Dr. Bortz discussed the map in some detail, pointing out that already the College has in most territories a resident Regent, and in all territories a Governor for each State. The Committee considered it premature to make specific recommendations, but it pointed out that obviously if the College continues to grow and postgraduate education continues to expand as it has in the recent past some arrangement as that presented should be taken under advisement.

Dr. Bortz also spoke of the advisability of having a section of the ANNALS OF INTERNAL MEDICINE devoted to a discussion of graduate education. Already the Executive Offices had been collecting all available data concerning postgraduate medical facilities in the United States and Canada, and publishing same periodically under the Editor's supervision. The Committee's suggestion was that a separate section on postgraduate activity or postgraduate news be maintained in the ANNALS. In this section might also be added recommendations for collateral reading, not abstracts of the literature, but an index to outstanding articles or books. Obviously medical literature is so vast that a great many worth while articles are overlooked by the individual whereas a department of this character would be a rather complete source and guide for all. Dr. Bortz, on behalf of the Committee, asked for specific instructions and advice from the Board of Regents in regard to the establishment of the course in Military Medicine.

Dr. Hugh J. Morgan, Chairman of the Regents' Committee on Educational Policy, reported as follows:

"This Committee recommends the adoption of the recommendations of the Advisory Committee on Postgraduate Courses, and suggests that the Chairman of that Committee be authorized to negotiate with the proper authorities in Washington for the establishment of a course in Military Medicine. I make that as a motion."

The motion was seconded by several and carried. Dr. Morgan continued his report:

"The Committee on Educational Policy has given much thought to ways and means of relating the activity of this College to the preparedness program and that will be discussed by Dr. James Alex. Miller in the report of the Committee on Survey and Future Policy. The suggestions of the Advisory Committee were, we felt, cer-

tainly pertinent. The matter of clinical fellowships, we believe should be referred to the Committee on Survey and Future Policy. The question of the geographical division of the country and the establishment of regencies to study the need of graduate training in the several regions and to provide for those needs is certainly an idea which has been in the minds of many. My personal reaction is that theoretically it would be an excellent plan; practically I doubt that the College could do much with it unless we had a full-time director of graduate training. We would like to have the Regents give thought to the advisability of employing a person with talents in that field to guide and direct the educational activity of the College. I can see how such a person would be of great help, for example, in relating the College to the preparedness program, in developing educational programs in hospitals attached to army camps, in helping develop local and regional programs sponsored by the College. Such a person might be useful in planning and organizing the program of the annual meetings. One of the chief functions of the College is to encourage and provide continuing education for people in Internal Medicine; maybe the time has come, or will very soon, unless great changes take place, when we should have a person who has the capacity and who is willing to devote his whole time to exploring the opportunities of the College, and I think they are very great and that we are not beginning to take advantage of all of them. This Committee has no further comments to make on the other suggestions from the Advisory Committee. The Advisory Committee has done a perfectly fine job in sampling or determining or finding out what the state of mind of the College members is relative to postgraduate training. We know what the members want and the present program will come very close to complying with those desires."

President Bruce said the two reports would be considered as one, and opened them for discussion.

Dr. Robert A. Cooke pointed out that neither Committee had stressed the importance of arranging courses far enough in advance, or in giving those who give the courses sufficient time. He said the whole matter should be arranged at least a year in advance, and even though the details of courses are not given, the courses should be selected, the locations and dates determined upon at least one year ahead.

The Secretary referred to correspondence especially from Associates inquiring to what degree these postgraduate courses are useful in the preparation for the American Board examinations. Due to the Regents having established the rule that all future Associates shall present certification as one of the prerequisites for advancement to Fellowship, Associates are inclined to assume that one of the purposes of the courses is to help them qualify for Fellowship. He suggested the possibility of some sort of coöperation and correlation between the College committees arranging and organizing these courses and the American Board of Internal Medicine. While no specific course of very short duration could be adequate to prepare a candidate for the Board examinations, it was conceivable, he thought, for a series of courses to be so organized that the candidate completing the entire series might readily obtain valuable aid toward preparation for the Board examinations.

Dr. Ernest E. Irons, Chairman of the American Board of Internal Medicine, said that the Board is deeply interested in any kind of properly administered graduate study and that such courses as offered by the College have accomplished a great deal in stimulating members and others to improve their medical equipment in one way or another. However, the type of preparation needed by younger men must necessarily include considerably more fundamental training than could be accomplished by these courses. If a man had this deeper fundamental knowledge of medical and clinical subjects, if he had a foundation and if he pursued a series of these courses, he would acquire a certain degree of additional information which would be of value and might conceivably help him with his examinations.

Dr. Irons continued by saying that as a fundamental part of the preparation for the Board examinations, these courses take a very secondary position. The Board has in mind the fundamental improvement and arrangement of standards of scholarship in medicine and anything along that line, of course, helps a little. The Board itself is not especially interested in examinations or diplomas or certificates. These seem to be necessary adjuncts or methods of determining whether a man has attained a certain quality of information and scholarship.

Summarizing, Dr. Irons repeated that the Board is deeply interested in other phases and other levels of graduate education, but would not wish to have even a series of courses regarded as adequate preparation for certification.

Dr. Francis G. Blake referred particularly to two suggestions in the report of the Advisory Committee on Postgraduate Courses: (1) the desirability of small groups, with not so many men enrolled; (2) the providing of suggested readings. If these two suggestions could be combined and if a group of not more than fifteen be enrolled in a particular course and in advance were provided with suggested readings and if when they come together for the course it is converted into a seminar type of exercise with discussions of what they have read, instead of just having didactic lectures, the value of these courses would be tremendously advanced.

Dr. David P. Barr, a member of the American Board of Internal Medicine, suggested that the courses arranged by the College should be primarily for internists who wish to refresh themselves on some particular phase of medicine. He felt that even short courses of only two weeks' duration may be very helpful. He said the American Board is dealing with men who are striving to be internists who are not yet trained and the Board must be alert for opportunities for long courses which last for six months, a year or two years. He felt the College properly should be interested in the problems of the American Board, because the efforts of the Board should furnish the College with its future members. He foresaw some opportunity of combination of effort between the College and the Board in making an orderly arrangement of these opportunities for younger men. For instance, the "Annals" has carried an index to courses available; the Board is trying to get lists of places where men can spend six months, a year or two years in training. The two efforts merge and become intimately associated.

Dr. Reginald Fitz endorsed Dr. Morgan's suggestion for a full-time director of educational opportunities of the College, feeling that the plan might develop into an important means by which all postgraduate educational opportunities could be correlated through this College.

Dr. Walter W. Palmer raised the question as to whether such a plan would in any way conflict with or duplicate the work of the Council on Medical Education and Hospitals of the American Medical Association.

President James D. Bruce expressed the opinion that it would not, because the objectives of the two organizations are identical—the improvement of the quality of medical service.

Dr. Irons was not enthusiastic about the suggestion, saying that if the College had had such a director it would not have had the very excellent report presented by Dr. Bortz, for if the College delegated this important work to some employee then no one else would do anything about it. He said the best thinking is done in these committees of the Board of Regents.

President Bruce referred to experience when a study was made of ways and means of improving the quality of medical service in the State of Michigan when there was much confusion with reference to the use of the term "postgraduate." He found satisfaction in the definition of "postgraduate" as a short intensive course designed to maintain a practitioner at a desirable level of efficiency, and "graduate" as applied to those longer, more academically arranged courses consisting of six

months or a year or several years, designed to equip a man for research, the practice of a specialty or for teaching.

Continuing, President Bruce said: "I cannot take the credit for setting up these suggested regional areas by the College, but the reason I had for locating the medical schools geographically was to add to our resources to see what we can count on in the way of a national program not only for the American College of Physicians, although I had them particularly in mind, but for the whole problem of education, and I have felt that any program that does not bring, such as we have been contemplating here, within the orbit of our planning the medical schools and their potential usefulness would not succeed in doing the things we have in mind. I also had in mind that local hospitals might very well tie up with the medical school and with the College. I would like to see the term 'postgraduate' applied to the short refresher courses and 'graduate' used with reference to those longer courses and provisions that qualify a man for the specialty of Internal Medicine."

Dr. Bortz: "The matter of training the doctor is very much a personal matter and degrees, per se, amount to little—the end is that the doctor be better trained. I do not think that Dr. Irons, or other members of the Board, intend to disparage the development and the interest in our courses. I think they want to avoid what happened in European countries before the World War, whereby a certain type of mind would go and put in a certain number of hours and at the end of two, three or six weeks of a course of instruction get a diploma, put it up in his office and call himself a specialist. I think the type of man in the American College of Physicians is not the type that relies on those superficial evidences to convince the public that he is adequately prepared to meet all the problems brought before him. The matter of allowing non-members of the College to take these courses should be decided today—whether or not the Board of Regents will permit men who are aspiring to membership in the College and who are properly qualified to benefit by membership in the College shall be permitted to take these courses. The Committee has in mind to recommend that qualified younger doctors, of whom there are an increasing number, be allowed, upon recommendation of the Governor or Regent or other properly qualified member of the College, to participate in the instruction. The men who have given the courses have remarked on the high type of men who have been taking the courses and on the interest and the serious point of view and the industry with which they have prosecuted their studies. It is evident that we must have more and more flexibility in offering opportunities for instruction. There are several institutions in the country that furnish opportunity for qualified men to take graduate courses. However, there is more of a demand than can be met. Several universities offer short courses and the Committee has been studying the question of whether or not for those men who cannot get away for six months or a year for continuous study, it might be possible to arrange with faculties at strategic points throughout the country to offer courses a little longer than our refresher courses—say for six weeks or two months during the summer. Incidentally, a number of our members requested that courses be offered in the summer when a number of faculty members would be free. . . . The Committee has discussed whether or not it might be possible to give a two months' course in St. Louis in the summer, a two months' course in the middle of winter at McGill, a two months' course at Yale in the spring and so on, so that a man could have the opportunity to take a two months' course in training and under supervision and advice from his teachers; and so that he could be given a course in selected reading that he could follow along and go back to his practice; then later, pursue another course of six or eight weeks in another center, and after following this program for two or three years, such a man would have a type of instruction that I believe could not be excelled. One of the sound principles of education is that of distribution in certain fields and concentration along one particular field. I think

it would be absolutely practical and very valuable to look into the future towards planning with a flexibility such as this kind of an arrangement would offer. Why could not a man spend twelve months in three years at one or two months at a time, going back to apply his instruction in his work, following the literature? Would he not have a type of training that even the American Board of Internal Medicine would have to admit was good? It is just a matter of having an organizational setup that will offer a man the greatest amount of instruction and experience in the shortest possible time."

Dr. Maurice C. Pincoffs, while expressing a full degree of sympathy with the postgraduate program and the accomplishments of the Committee, referred to the major part of the work being done by the institutions where the courses are offered. The College, he said, must take into account what the resources of these schools may be. He did not consider it feasible to undertake to organize postgraduate courses at one institution as a permanent program during the summer months, for instance. The great difficulty of extensive postgraduate work is that it involves the reorganization of schools, a very much enlarged budget and enlarged faculty, and very fundamental changes. Dr. Pincoffs advocated that in view of the large demand for these postgraduate courses among members of the College, that registration be largely restricted to the members of the College and that the institutions offering the courses be consulted before any non-members shall be admitted. The Secretary explained that this had been the guiding principle since the courses were first organized, except that when it became apparent there might be vacancies in any course, qualified non-members planning eventually to become members of the College or to be certified by one of the boards were admitted, subject to the approval of the director of the course.

On motion by Dr. Pepper, seconded by Dr. Cooke, and regularly adopted, it was RESOLVED, that non-members be not admitted to the Postgraduate Courses except when it shall be obvious to the Executive Secretary that there will be vacancies, and then only upon recommendation from a Regent or Governor, with the approval of those giving the courses.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Walter W. Palmer, and regularly carried, it was

RESOLVED, that the recommendations of the Advisory Committee relative to the Postgraduate Courses be adopted.

On motion by Dr. Hugh J. Morgan, seconded by several and carried, it was

RESOLVED, that the suggestions relative to clinical fellowships and relative to the appointment of a director of postgraduate training be referred to the Committee on Survey and Future Policy for consideration.

The following report was presented by Dr. Ernest E. Irons, Chairman of the American Board of Internal Medicine:

- "(1) The Board has certified a total of 2,365; of these 553 were certifications by examinations;
- "(2) The Board now has a uniform working agreement with each of four sub-specialties, namely, Cardiovascular Disease, Gastro-enterology, Allergy and Tuberculosis. These agreements provide: (a) that all certificants, whether interested in Internal Medicine in general or in, for example, Cardiovascular Disease as a sub-specialty, shall pass the examinations of the American Board and be first qualified as internists; (b) qualification in the sub-specialty will be determined by examination by an accredited representative of the sub-specialty named by the standing committee of the sub-specialty. This examiner will sit with the member of the Board; (c) the examination will be conducted only at the time of other examinations of the Board. Each sub-specialty has named a committee to coöperate with the Board; (d) there will be no sub-

boards; all certifications will remain under the complete supervision of the American Board;

- " (3) A joint committee of coöperation between the College, the Council on Medical Education and the Board is functioning in the investigation and recognition of hospital residencies;
- " (4) The Board wishes to go on record as favoring the use of preceptors by candidates in their preparation for the examination of the Board. The selection of satisfactory preceptors is, in the opinion of the Board, a question which must be determined by the Board in each individual case;
- " (5) The bank balance of the Board, as of December 1, is \$22,115.52. The Board considers that this balance should not be increased and proposes to consider a reduction in the fee paid by candidates for examination. At present this fee is \$50.00. The fee is already considerably less than that of a number of the other Boards. The Board hesitates, however, to take any action at the moment until some experience has been gained as to the increased expense which will be entailed by the use of examiners in the sub-specialties. Such experience should be available within perhaps a year.

Respectfully submitted,

AMERICAN BOARD OF INTERNAL MEDICINE,

ERNEST E. IRONS, *Chairman*"

Commenting upon the above report, Dr. Irons said: "The use of the term 'Preceptor' and the approval in certain instances of such a preceptor is not intended to do away with any of the fundamental training that candidates receive, but the latter part of such preliminary training might be attained by a man working with a recognized, careful internist who has the proper ideals of scholarship and under whom this prospective candidate may obtain a wide and valuable knowledge of clinical medicine. In any case, there is no thought in the mind of the Board to reduce in any way the quality of effort put forward by the candidate."

Dr. Irons further reported that conferences had been held with accredited representatives of several of the sub-specialties, and temporary or preliminary statement of aims had been drawn up, a tentative agreement reached and sent back to the sub-specialty bodies. The group or groups accredited for each sub-specialty appointed a committee to supervise the appointment or furnishing of a list available to take examinations, who would have authority to represent that particular sub-specialty in the work of the Board. The committee, usually consisting of three, in each case had been confirmed by the American Board and the names of the members of the committee will appear on the stationery of the Board. Candidates who pass these sub-specialty examinations, if desired, may have special notation of proficiency included on their regular Board certificate.

By resolution regularly adopted, Dr. Irons' report was accepted.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported that Dr. Kenneth Evelyn, to whom a Research Fellowship had been awarded two years ago, had been called to active military service and probably will be unable to take advantage of the award, and the Committee recommended that the funds be liberated, with the understanding that if by chance Dr. Evelyn should wish to re-apply sometime in the future, there would be no obstruction to his doing so.

On motion by Dr. C. H. Cocke, seconded and regularly carried, it was RESOLVED, the funds appropriated, \$1,800.00, for a Research Fellowship for Dr. Kenneth Evelyn be liberated.

Dr. Barr continued his Committee report. The Committee had considered fifteen candidates for 1941 Research Fellowships. These candidates had a wide distribution—University of California, Washington University, Johns Hopkins University, Ohio State University, Vanderbilt University, University of Maryland, University of

Chicago, New York University, University of Southern California, George Washington University, University of Colorado and Northwestern University. The Committee, because of the cancellation of the Fellowship to Dr. Evelyn, nominated three candidates, whose credentials were reviewed in detail by Dr. Barr.

On motion by Dr. Barr, seconded by Dr. William D. Stroud, and regularly carried, it was

RESOLVED, that Research Fellowships in the amount of \$1,800.00 each be awarded to Dr. Allan Bass, Nashville, Tenn., Dr. Rulon Rawson, Boston, Mass., and Dr. William Arrowsmith, St. Louis, Mo., beginning July 1, 1941.

Dr. Barr then reported on the progress of those who now hold Research Fellowships of the College, Dr. Robert Williams, Dr. Lewis Dexter, Dr. Harold Magnuson and Dr. Morris Tager. Letters concerning their work were passed around for reading by the Regents.

Thereafter, Dr. Barr reported that the Committee had distributed one hundred and sixty inquiries to Regents, Governors, medical teachers and others concerning nominations for the John Phillips Memorial Award. Fifty candidates were suggested. After a discussion of the various guiding principles the Committee had followed, Dr. Barr specifically presented the following recommendation:

"The Committee on Fellowships and Awards unanimously recommends to the Board of Regents that the John Phillips Memorial Medal for 1941 be awarded to Dr. William Christopher Stadie, Associate Professor of Research Medicine at the University of Pennsylvania. Dr. Stadie was born in New York City on June 15, 1886. He received a degree of Bachelor of Science at New York University in 1907 and the degree of Doctor of Medicine at the College of Physicians and Surgeons at Columbia University in 1916. He was an interne at the Presbyterian Hospital in New York from 1916 to 1918, and an Associate at the Rockefeller Institute from 1918 to 1921. He was Assistant Professor of Medicine at Yale University from 1921 to 1924. Since 1924 he has been associated with the John Herr Musser Department of Research Medicine at the University of Pennsylvania.

"His early investigative work was conducted under the tutelage of Dr. Donald D. Van Slyke and was concerned chiefly with the determination of gases in the blood and the relation of gases to clinical acidosis and to cyanosis. He was also interested in studies on the formation and fate of methemoglobin. He was in large part responsible for the construction at the Rockefeller Institute of an oxygen chamber for the treatment of anoxemia in pneumonia. With his associates at Yale and at the University of Pennsylvania he conducted detailed studies on oxygen-, acid-, and base-combining properties of blood and upon the rôle of carbamino compounds in the transport of carbon dioxide by blood.

"Dr. Stadie's more recent studies have been concerned with the fat metabolism in diabetes. In the course of this work he has shown that the previous concepts of the catabolism of fat are not tenable, that the beta oxidation theory of Knoop and Dakin, which postulates that each molecule of fatty acid yields one molecule of ketone does not account for the actual amount of ketone produced by the liver. He has shown that the catabolism of fat is such that each molecule of fatty acid yields approximately four molecules of ketone; that ketone formation is accomplished in the liver and that ketones are utilized in the muscles. He has demonstrated that ketonemia and ketonuria will occur only when the production exceeds the utilization; furthermore, that the complete utilization of fats is limited under any given set of physiological conditions. This concept renders unnecessary the theory long and firmly held that complete combustion of fat is dependent upon the simultaneous combustion of carbohydrate, which has been the basis of the elaborate calculations on the ketogenic-antiketogenic ratio in the practical management of diabetes.

"Incidentally, Stadie's work has settled another long standing controversy in metabolism and has shown conclusively that the production of glucose in diabetes can

not be accounted for by the conversion of fat into carbohydrate. To many who are most informed in the intermediary metabolism of food stuffs and in the clinical study of diabetes, Stadie's investigations are regarded as of fundamental importance and among the significant contributions of our time. It appears to the Committee that they will be reflected in clinical thought and in practical dietetics.

"The Committee recommends that the award be made for Stadie's significant contributions to the knowledge of cyanosis, anoxia and the physical chemistry of hemoglobin, and more especially for his recent studies on the fat metabolism of diabetes mellitus."

On motion by Dr. Barr, seconded and regularly carried, the recommendation was unanimously adopted.

Dr. William D. Stroud, Chairman of the House Committee, reported as follows:

"A meeting of the House Committee was held at the College Headquarters on October 18, 1940, with full Committee in attendance, including Chairman Stroud, T. Grier Miller and Harry B. Wilmer. The Committee approved and recommended the following:

- (1) That the Chairman address a letter to certain Fellows of the College, such as Orrin S. Wightman, Kenneth Taylor, Harold W. Dana and Sir Frederick Banting, who are artists or have a particular interest in art, enclosing a photograph of the Board Room showing the panel space above the fireplace, and asking for suggestions of an appropriate subject or painting;
- (2) That Dr. T. Grier Miller and Dr. Harry B. Wilmer contact certain individuals whom they thought might be conversant with suitable and appropriate suggestions of appropriate subjects;
- (3) The Committee approved expenditures of \$150.00 for necessary roof repairs;
- (4) That Dr. William D. Stroud, as Chairman, communicate with Mr. Charles J. Eisenlohr concerning the possibility of his establishing an endowment in memory of his sister, Marie Eisenlohr, for the maintenance of the College grounds.

"The Committee reports that the Chairman addressed a letter to various Fellows of the College, as suggested in (1) above, but has obtained no helpful or specific suggestions; and that the Chairman communicated with Mr. Eisenlohr concerning the possibility of establishing an endowment for the maintenance of the College grounds, and received a courteous reply to the effect that he appreciated the merits of the request, but due to more urgent requests for other philanthropies, he felt unable to contribute the fund to the College.

Respectfully submitted for the Committee,

DR. WILLIAM D. STROUD, *Chairman*"

On motion by Dr. Stroud, seconded and regularly carried, the report was adopted.

Dr. Walter W. Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported as follows:

"The Committee met with Dr. Maurice C. Pincoffs, Editor, at 2:00 p.m., Saturday, December 14, 1940. The Committee believes the ANNALS under Dr. Pincoffs' direction accomplishes its purpose admirably and has no suggestion for any changes in policy. We would report on a few minor matters which came before the Committee:

- "(1) At present the number of pages a year amounts to about 2,400, which, if bound in a single volume, is unwieldy. Already the Librarian of New York University has requested two title pages and two indices for purposes of separating the present yearly issues into two bound volumes.

"The Committee recommends that the ANNALS be issued in two volumes a year. This can be done at slight additional cost.

" (2) At its meeting last spring the Board of Regents voted to publish in the ANNALS, from time to time, announcements of postgraduate facilities. When this motion was passed no provision was made as to supervision of the lists, collection, etc.

" Your Committee believes that all material connected with postgraduate activities and facilities to be published in the ANNALS should be placed under the control and supervision of the Advisory Committee on Postgraduate Courses, and so recommends.

" (3) Mr. Loveland, the Executive Secretary, informed the Committee that the postage on the ANNALS, when sent to foreign countries, other than Canada, and those in the Postal Union, cost \$1.52 a year.

" Although the number of subscriptions affected is small, perhaps 100, the Committee recommends that the subscription rate to the high postal rate subscribers be increased from its present rate of \$7.50 to \$8.00 a year.

Respectfully submitted,
COMMITTEE ON ANNALS OF INTERNAL MEDICINE
WALTER W. PALMER, *Chairman*
DAVID P. BARR
REGINALD FITZ "

On motion by Dr. Palmer, seconded and regularly carried, the report was adopted.

Dr. Francis G. Blake, Chairman of the Committee on Scientific Exhibits, reported that two meetings of that Committee had been held to consider and discuss the feasibility of the College initiating scientific exhibits at its annual meetings. After due deliberation, the Committee recommended that the College shall not undertake at the present time the addition of scientific exhibits at its annual meetings. Reasons underlying the recommendation, briefly, were: the addition of a scientific exhibit would require a considerably larger amount of space which might further limit the cities where meetings of the College could be held; a scientific exhibit might introduce a certain amount of competition with the rest of the program and might interfere somewhat with attendance of the program; in view of the excellent and expanding development of postgraduate work any available money for additional expenditure might more profitably be spent on the postgraduate work than in adding another scientific exhibit which in reality is in no sense a novelty, since several excellent scientific exhibits are already being held; a really large and useful scientific exhibit, coming with only a very brief period before the scientific exhibits of the American Medical Association, might offer certain serious difficulties in obtaining adequate exhibits which would not either forestall or conflict with the American Medical Association's exhibits.

On motion by Dr. Blake, seconded and regularly carried, the report was adopted.

Dr. William D. Stroud presented the Treasurer's report:

" The present holdings of the College amount to, at book value, \$212,246.66 (\$124,847.69, Endowment Fund; \$87,398.97, General Fund). The total market value at current prices is \$211,921.26 (depreciation, \$325.40).

" The holdings of the College reported one year ago, at book cost, were \$177,252.56, and a market valuation of \$174,658.75.

(At this point Dr. Stroud read a full list of purchases and sales of securities from January 1, 1940, to date, showing purchases of \$43,174.56 for the Endowment Fund; \$37,493.11 for the General Fund; total purchases, \$80,667.67.

Total sales amounted to: Endowment Fund, \$17,964.86; General Fund, \$18,851.02; total sales, \$36,815.88.

Purchases exceeded sales by \$43,851.79; the net profit on trading was: Endowment Fund, \$317.31; General Fund, \$76.87; net trading profit, \$394.18.)

"As directed by the Board of Regents at one of its meetings in Cleveland, April, 1940, approximately \$25,000.00 was transferred from the General Fund to the Endowment Fund. On December 1, 1940, Cash in the General Fund amounted to \$17,534.71 and in the Endowment Fund amounted to \$1,499.38. It is estimated that at the end of the current year, December 31, 1940, the balance transferred to present worth will be approximately \$29,000.00, bringing the total present worth of the College to approximately \$290,000.00.

"During the year a reduction in real estate assessment of the College Headquarters from \$43,600 to \$39,700 has been obtained, which should result in a 9% decrease in taxation.

"During the year, 1940, the Highland National Bank, Pittsburgh, paid a dividend of \$467.41 on account of the balance owing us from the time of the 1931 bank closures. The dividend was accompanied by a statement that this was the final dividend that we may expect, resulting in a loss to the College of \$2,032.45, this amount representing the balance of our original equity.

"The Exchange National Bank, Pittsburgh, also one of the closed banks, has not finally settled up its account, and the balance still owing to us is \$1,166.14.

"The Bank of Pittsburgh National Association has previously refunded our entire original deposit, but there remains a balance of assets to be distributed to former creditors in the form of interest on claims since the date of suspension of said bank, amounting to 11.521% of the face amount of the original certificate. The Shareholders Committee on July 1, 1940, recommended that creditors, in order to facilitate the final closing of the affairs of the bank, accept the proposal embodied in the following resolution, and the Finance Committee voted its temporary approval, subject to the formal adoption of the resolution by the Regents, which we now recommend:

"RESOLVED, that the proper officers of this corporation be, and they hereby are, authorized and directed to execute and deliver under the seal of this corporation 'Conditional Assignment of Claim,' the effect of which is to waive the right to all interest on the deposit of this corporation in The Bank of Pittsburgh National Association, Pittsburgh, Pennsylvania, in excess of 11.521% on the first \$1,000.00 and 3.45% on the balance of the face amount of the receiver's certificate evidencing this claim.

Respectfully submitted,

WILLIAM D. STROUD, *Treasurer.*"

On motion by Dr. Stroud, seconded and regularly carried, the Treasurer's report was adopted and approved.

Dr. Roger I. Lee, Chairman of the Committee on Finance, presented the following report, after distributing copies of the proposed budget for 1941:

"The Committee on Finance held a meeting at the College Headquarters on Saturday, December 14, with Drs. Lee, Chairman, Pepper and Treasurer Stroud present. Dr. Stone was unavoidably detained.

"The financial condition of the College continues to be excellent—for the past year it produced a surplus of approximately \$19,000.00. It might be noted in passing that the commercial exhibit produces about \$15,000.00 and if that money is not available, the College budget would approximately balance.

"The invested funds of the College seem to be in excellent condition. There is an increased percentage of our holdings in bonds, now amounting to 54%—of somewhat over 30% in preferred stocks and about 13% in common stocks. The Finance Committee requested the Treasurer to investigate the desirability of a possible change in the investment counsel. This is entirely for purposes of economy.

"The Committee scrutinized the budget and is, as always, very much impressed with the remarkably accurate estimates of the Executive Secretary. . . . In the budgets presented, the Committee thought there should be an increase in the General Chair-

man's budget of \$300.00; in the Executive Secretary's budget of \$372.30, for the specific purpose of increasing the salary of the Assistant to the Executive Secretary by \$200.00, a bonus of \$50.00 to the caretaker of the building, and a repayment to the College Historian of \$122.50 for funds expended personally.

"The Committee discussed the question of travel expense. It was the opinion of the Committee that air travel should be recognized as a form of travel and the adoption of the method of air scrip brings it in general in line with the expense of railroad travel.

"The suggestion of a member that members upon reaching the age of sixty-five be allowed to become Life Members for \$50.00 was discussed. It might represent a very large continuing item in regard to supplying the journal, and the Committee voted not to recommend the establishment of this class of Life Membership.

"The Committee voted to recommend to the Regents that Fellows and Associates on active service with the armed forces pay at the same rate as the regular members of the Army, Navy and Public Health Services; that is, \$10.00 admission fee and \$10.00 dues. The Committee also recommends that individual cases receive sympathetic consideration through the usual channels.

"The Committee voted that the Executive Secretary study the problem of pensions, compulsory savings, etc., of the College personnel and the problem of establishing reserves for that purpose.

Respectfully submitted,

COMMITTEE ON FINANCE

ROGER I. LEE, *Chairman.*"

Thereafter the following specific resolutions were adopted:

RESOLVED, that the budget for 1941 as presented (with an estimated income of \$113,800.00, and an estimated expenditure of \$87,144.00) to the Board of Regents be increased by \$672.30. (Secretary's Note: Total appropriations for 1941 expenditures, as subsequently made, amounted to \$100,566.30.)

RESOLVED, that the budget in general, as presented, be approved.

RESOLVED, that the proposal to establish a Life Membership fee of \$50.00 at age sixty-five be not adopted.

RESOLVED, that Fellows and Associates on active service with the armed forces have reduction in fees and dues at the same rate as regular members of the Army, Navy and Public Health Services, with the additional recommendation that individual cases receive sympathetic consideration through the usual College channels.

RESOLVED, that the report of the Committee on Finance be adopted as a whole.

Dr. James Alex. Miller, Chairman, presented the following report of the Committee on Survey and Future Policy.

"The Committee on Survey and Future Policy held a meeting at the College Headquarters on Saturday, December 14, at 4:00 p.m., with the following members present: Charles H. Cocke, Roger I. Lee, Hugh J. Morgan, George Morris Piersol and James Alex. Miller, Chairman.

"The financial situation of the College was presented by Dr. Lee. In discussion, it was suggested, in making estimates for future expenditures, that it should be borne in mind that the income might be affected (1) by diminution of dues for Fellows inducted into Army Service and (2) by possible diminution of new Fellows because of future requirements for certification for advancement from Associateship to Fellowship; also that increased expenditures might be anticipated, first, by desirable expenditures in connection with the defense program, and, second, by the development of the educational program.

"Size of the College:

"The present size of the College is approximately 3,200 Fellows and somewhat over 1,200 Associates. It was recommended by the Committee that the Regents take into consideration the probability that approximately this size might have to be considered as the desirable permanent membership on account of the restrictions in available meeting places for Sessions of greater size.

"This Committee has no definite recommendations as to exact numbers, but feels that soon a definite principle must be laid down by the Regents, and our Committee intends to make a special study of this situation in connection with actuarial expectation of life of our present membership and other factors involved, and to report to the Board of Regents more in detail at a subsequent meeting.

"Reduction of Dues for Fellows Inducted into Army Service:

"The Committee recommends that the Board of Regents authorize a reduction of dues for such Fellows on the basis of the present Army dues, namely, \$10.00 Initiation Fee and \$10.00 Annual Dues. Requests for total exemption from dues should be considered and decided upon by the circumstances in each individual case.

"Coöperation with the Defense Program:

"It was the consensus of opinion in this Committee that the College should adopt a generous attitude toward expenditures in coöperation with the defense program, instead of continuing to accumulate the full amount of the annual surplus.

"Very careful consideration was given to Dr. Pepper's memorandum on behalf of the Medical Committee of the National Research Council. In this memorandum, Dr. Pepper made three specific suggestions:

"(1) That the College make formal application for membership in the National Research Council; this recommendation was approved and is recommended to the Board of Regents.

"(2) That the College make an appropriation to provide assistance for a survey of all the internists of the country, which is being made at the request of the Army Medical Service.

The Committee recommends that \$2,500.00 be appropriated to the National Research Council specifically for this purpose.

"(3) Dr. Pepper suggested an additional general appropriation for the use of the Medical Committee of the National Research Council for a total amount possibly up to \$10,000.00.

The Committee has no specific recommendation to make in regard to this suggestion, but was enthusiastically sympathetic to the great service that this Medical Committee was rendering under Dr. Pepper's Chairmanship, and notes with pleasure that all the members of this Committee are Fellows of the College. It seemed, however, to the Committee that possibly it might be desirable to put the responsibility for the general support of the National Research Council up to the Government, and that the College favorably consider specific requests for support of definite objects in the program of the Medical Committee as they might be presented through the Chairman, Dr. Pepper. The Committee felt it desirable that this whole matter should be fully discussed by the Board of Regents and a general policy adopted.

"It was brought to the Committee's attention that the Army is contemplating the establishment of 70 general hospitals, for which a large medical staff, possibly 10,000 medical officers, might be required, a large proportion of which would be young men.

"Your Committee recommends that the Regents consider the organization of courses of instruction in Internal Medicine for this personnel, to be organized locally

through Fellows in the College residing in and near each hospital, thus enabling the year of service to these medical officers to become a year of postgraduate education, and that possibly such a course might be considered as a resident year counting toward the qualifications for certification by the American Board of Internal Medicine.

"Your Committee recommends the Board of Regents authorize the appointment of a committee to prosecute this idea with the appropriate authorities.

"Other Items in the Postgraduate Education Program:

"The Committee studied with great interest the admirable report submitted by the Advisory Committee on Postgraduate Courses. We wish to emphasize particularly importance of extending the plan for special courses in preparation for the examination for certification by the Board of Internal Medicine among the Associate Fellows.

"It also suggests the consideration by the above committee of the problems of industrial medicine as they relate to Internal Medicine and as opposed to the present emphasis on surgery.

"Exhibits:

"The Committee considered the question of the Commercial Exhibits, and it was brought out in discussion that the growing size of these exhibits tends to restrict holding of Annual Sessions to a few cities where sufficient space is available. The Committee, therefore, suggests that the Regents consider the possibility of reducing the size of these exhibits, possibly through increasing the rental rates, in this way automatically diminishing the size and improving the quality.

"Committee on Credentials:

"It was brought to the attention of the Committee that the individual members of the Committee on Credentials carry a very heavy load, involving a great deal of home work in addition to their arduous duties in connection with their regular meetings.

"The suggestion was made that possibly an honorarium should be allowed for the members of the Committee on Credentials. Your Future Policy Committee is of the opinion that such action would be undesirable, but would suggest the Board of Regents authorize a more generous policy toward the allowance for expenses for members of the Credentials Committee at the time of each Annual Session.

"Clinical Fellowships:

"Your Committee considered the desirability of the College establishing one-year Clinical Fellowships in addition to the Research Fellowships, and recommends that the Board of Regents consider this suggestion, which appears to your Committee to be desirable.

"State and Regional Meetings:

"Your Committee notes with great pleasure the development of this plan under the sponsorship of the Board of Governors, 13 such meetings being held in 1940. We recommend that the Board of Regents express an appreciation of this service on the part of the Board of Governors and urge the further expansion of this program for regional meetings, and also inasmuch as Officers of the College are frequently invited to participate in these meetings and as their presence at such meetings is undoubtedly of great benefit to the College, that the Board of Regents authorize the allowance of traveling expenses for such Officers, and also that they authorize the Executive Office to meet incidental expenses, such as printing and postage, which are incurred in connection with such meetings.

"The History of the College:

"Your Committee is greatly impressed with the character and value of the Volume on the History of the College, which has just been published under Dr. William Gerry Morgan's Editorship.

"It would seem to your Committee, however, that the edition thus far authorized is too small and should be increased, and that the Board of Regents authorize the free distribution of a volume of this History to all Fellows and all Associates, and that also for the next few years a copy of the History be given free to each new Fellow and Associate when elected.

Respectfully submitted,

COMMITTEE ON SURVEY AND FUTURE POLICY

DR. JAMES ALEX. MILLER, *Chairman.*"

Dr. Miller opened discussion concerning the College making formal application for membership in the National Research Council.

Dr. David P. Barr asked for a statement as to exactly what membership implies. Dr. O. H. Perry Pepper reminded the Board that the National Research Council was established by the late President Woodrow Wilson. Many of the societies that formed the Congress of American Physicians were made use of. Since then additional societies have been added at their own request, until now there are 17. There are no duties on the part of these societies other than attendance by representation at the annual meeting. Dr. Pepper named most of the societies having membership in the Council. He said the Council was merely a holding corporation calling upon these representatives to assist them in their deliberations. The National Research Council was established as an advisory body to assist the Federal Government in any way upon request. Its activities have recently been revitalized by requests from the Surgeons General. The National Research Council has many divisions, including a medical division. Dr. Pepper expressed the opinion that it is appropriate, since there are so many Fellows of the College working with the National Research Council on its committees, that this College should join with the group.

On motion by Dr. Miller, seconded by Dr. Piersol and regularly carried, it was

RESOLVED, that the American College of Physicians shall make formal application for membership in the National Research Council.

On motion by Dr. Miller, seconded by Dr. Pepper and regularly carried, it was

RESOLVED, that the Board of Regents appropriate from College funds a sum of \$2,500.00 to the National Research Council for general assistance in a survey of internists.

Dr. Miller then opened for discussion an additional general appropriation for the use of the Committee on Medicine of the National Research Council for a total up to \$10,000.00, suggesting that the Regents should adopt a policy as to whether the appropriation should not be made according to specific needs, subject to the approval of some committee, such as the Executive Committee.

Dr. Pepper said he was in entire sympathy with the idea that the appropriation be made for specific purposes and only with the approval of the Officers or the Executive Committee of the College, but his primary suggestion had been simply that there was a big activity going on, that Government support might not be sufficient, that the activity of the Medical Division was being carried on very largely by members of this College and that this College might want to make a gesture and actually do something more for national defense and that it could be assured that any appropriation would be spent usefully. Dr. Pepper presented a chart which showed that all members of the Committee on Medicine are Fellows of the College and 60 per cent of the members on the sub-committees of the Committee on Medicine are members of this College. Dr. Pepper said the purpose for which this money would be spent would be specific support of research and he advocated the appropriation of a maximum sum against

which, with the approval of the Committee on Medicine and the approval of the Officers of this College, funds could be drawn for specific purposes. He referred to a number of research problems on the agenda for various committees and sub-committees, including one for the preparation of a manual to take care of all phases of the study, diagnosis and treatment of a possible influenza epidemic. Dr. Pepper further said that all the appropriation might not be spent, while on the other hand there might arise great needs for the whole amount, and if the appropriation is made the regulations governing its expenditure be specific and simple, so that needed funds would be available quickly.

President Bruce expressed his sympathy with anything that the College may do, either through its membership or its influence or through its funds at this time in the general program of preparedness. He suggested two methods by which the College could give an outward and visible sign of its support: (1) an actual appropriation to the National Research Council of a sum of money earmarked for this particular purpose; or (2) that the College set aside a certain sum of money to be available on the request of the Committee on Medicine and the decision for expenditures from that fund be left in the hands of the Executive Committee for this specific purpose.

On motion by Dr. Pepper, seconded by Dr. William D. Stroud, the following resolution was presented:

RESOLVED, that the Board of Regents of the College appropriate a sum of \$10,000.00, which shall be available for specific purposes of the Committee on Medicine of the Division of Medical Sciences of the National Research Council, on recommendation of that Committee and the approval of the Executive Committee of the Board of Regents during the year 1941.

In the discussion that followed, Dr. Barr expressed himself as thoroughly in sympathy with the intent of the motion, but said that during the past few months the National Research Council had been expecting from the President of the United States a special fund of a quarter of a million dollars. For reasons not apparent the money had not been forthcoming. He understood that the funds had now been assigned. If the appropriation by the College now under consideration had been available earlier, Dr. Barr thought it might have been dissipated, in order to hasten certain things which would have been cared for in due time by the Government. He mentioned this purely as a possible danger.

Dr. Pepper reaffirmed that the quarter million dollars had been made available. One of the other committees had already turned in a budget for research requesting \$170,000.00. Dr. Pepper did not think the presence of \$250,000.00 an argument against the College doing something. He expressed the opinion that if Federal funds become available the Committee on Medicine would use that in preference to the sum appropriated by the College.

Dr. Hugh J. Morgan inquired if the Committee on Medicine was asking for this appropriation from the College as a sort of emergency fund for its convenience, to be replaced or repaid, perhaps, from Government funds if and when such Government funds become available.

Dr. Pepper expressed doubt that that would ever be feasible. If the College shall appropriate this fund and it is spent, Dr. Pepper thought there will be little likelihood of it being refunded; if the appropriation is not used, it will remain in the hands of the College.

Dr. Maurice C. Pincoffs said there are a number of purposes included in the program of the Committee on Medicine that fall well in line with our regular policy of supporting research. In that field the College is putting forth a special effort and drawing more freely than usual on its resources because of the emergency. For such specific objectives in the field of research especially which could not be covered by available funds which have an element of urgency, the College could be of great help,

said Dr. Pincoffs. He thought it would be rather a departure if these funds were to be drawn upon for specific objectives outside of that field and inquired whether Dr. Pepper had in mind that the requests might be in that specific field or not. Dr. Pepper replied that after thinking over the proposal more carefully, he did not feel that the appropriation by the College should be dissipated for such things as travel expenses, unless there should be some peculiar situation, such, for example, as the necessity of having one of the committee chairmen travel to an area in which some emergency had arisen, or, for example, the publication of some particular needed manual for which other funds might not be available. However, Dr. Pepper expressed the hope that the appropriation could be largely restricted to research.

Dr. Walter W. Palmer expressed the opinion that to use College funds collected from its membership for a purpose of this sort, however worthy, may conceivably establish a bad precedent. He inquired if any other societies that are members of the National Research Council have offered to make contributions along the line suggested. Dr. Pepper answered in the negative, but said he had hoped the College would be the leader and that this might establish a precedent for other societies or groups to follow. He pointed out that other institutions are giving money indirectly through lending their men and their laboratories. Dr. Pepper expressed the opinion that the membership would read of such an activity by the College with pride rather than objection. He again emphasized the fact that the appropriation would be made specifically for the needs of the Committee on Medicine.

Dr. Francis G. Blake assured the Regents that they would need to have no worry about safeguarding the use of the money for the purpose for which they desire it to be spent, because all the grants for the Division of Medical Sciences are always on well defined votes for specific things and are used meticulously for the particular purposes for which they are given.

Dr. Hugh J. Morgan said he would like to feel certain that the College was not appropriating five or ten thousand dollars to a million-dollar project which otherwise is going to be paid for by tax money. He did not like the idea of the College contributing five or ten thousand dollars to an enormous pool, all the rest of which is coming from Government tax money. On the other hand, he expressed appreciation of the importance of the Committee having a fund available for emergencies that may develop for which the ponderous Government machinery for supplying funds would delay action.

Dr. Pincoffs opposed the responsibility of approving individual requests being turned over to the Executive Committee and favored some definite action by the Board of Regents itself. He was in favor of the proposed appropriation, providing that the request shall be of an emergency nature in which the element of time is concerned and for which no other funds are available. After all, he said, it is for the cause of Internal Medicine as applied not only to the Army as an institution but to the country as a whole, and while \$10,000.00 is not a very large sum to make available, part of it probably wouldn't be used if it is restricted to such emergency projects. He said the College had a responsibility to safeguard funds entrusted to it, but that he believed that the body of the College would thoroughly approve of some decisive action in the present situation.

Dr. Pepper's original motion was put and unanimously carried.

Dr. Miller then returned to further details of the report of the Committee on Survey and Future Policy.

On motion by Dr. Paullin, seconded and regularly carried, it was

RESOLVED, that the Board of Regents authorize the appointment of a committee to investigate the feasibility of establishing courses of instruction in Internal Medicine for the personnel of general hospitals to be established by the Army, courses to be organized particularly for the younger men of the staff by local Fellows of the College

residing in and near each hospital; the committee to consult the proper authorities and report back to the Board of Regents.

Also, on motion by Dr. Miller, seconded and regularly carried, it was

RESOLVED, that the suggestion of diminishing the size of the Technical Exhibits be referred to the Committee on Advertising and Exhibits for study and a later report.

On motion by Dr. Miller, seconded by Dr. Paullin and regularly carried, it was

RESOLVED, that honoraria be not established for members of the Credentials Committee, but that in appreciation of the immense amount of time that is required by members of this Committee not only through the year, but preceding the opening of the Annual Session, a more generous policy be adopted in regard to the payment of their expenses.

On motion, seconded and regularly carried, it was

RESOLVED, that the matter of establishing clinical fellowships be considered extremely desirable, but that the Committee on Survey and Future Policy continue to investigate the possibilities.

On motion by Dr. Miller, seconded by several, and unanimously carried, it was

RESOLVED, that the Board of Regents shall compliment the Board of Governors for what has already been accomplished and urge the further expansion of the program for regional meetings, and the Executive Office shall be authorized to meet incidental expenses in connection with such meetings and also to give an allowance for traveling expenses to Officers of the College who are asked to attend these meetings.

On motion by Dr. Miller, seconded by Dr. Irons, and regularly carried, it was

RESOLVED, that an additional appropriation of \$1,800.00 be made to cover the re-printing of approximately 1,800 additional copies of the College History, to provide an adequate number to distribute free to all Fellows and Associates of the College in good standing, as well as to provide for the next few years a copy of the History to be given free to each new Fellow and Associate when elected.

Dr. William D. Stroud, Treasurer, reminded the Regents that the College has been running for the past few years with a surplus of approximately \$20,000.00 per year and that the additional appropriations just authorized amounted to some \$15,000.00; in fact, additional appropriations over the 1940 budget amounted to between \$15,000.00 and \$20,000.00, and with the prospects of a smaller technical exhibit at the Boston Session, the 1941 surplus might readily be very small, if any at all.

The Executive Secretary, Mr. Loveland, also pointed out that the approval of payment of traveling expenses for all officials of the College to regional meetings when invited would be a growing expense, because of the growing popularity of these meetings. He expressed full approval of a plan to make regional meetings more effective, but pointed out that in view of the fact that no specific appropriations were made for this purpose, although he had been authorized to pay such expenses, his budget for 1941 might be overdrawn. He suggested that the cost of the College Headquarters for regional meetings would probably reach at least \$500.00 for 1941.

On motion by Dr. Charles H. Cocke, seconded by Dr. William D. Stroud, and regularly carried, it was

RESOLVED, that the report of the Committee on Survey and Future Policy be accepted as a whole.

On inquiry by the Executive Secretary, the Regents affirmed that the adoption of the above resolution carried with it an additional \$500.00 appropriation for regional meetings.

Dr. George Morris Piersol, Chairman of the Committee on Advertising and Exhibits, reported that in accordance with the previously established policy of the Committee, it had scrutinized the advertisers in the ANNALS and had passed upon all new applicants for admission to the exhibit invitation list. All drugs accepted for advertising in the ANNALS had been required to be accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

Dr. William B. Breed, General Chairman of the Twenty-fifth Annual Session of the College to be held in Boston, April, 1941, reported on preparations for entertainment and the program of clinics and panel discussions. He distributed a tentative program of the panels and of the clinics. He emphasized that Boston is very keen to entertain the College.

President Bruce then distributed copies of the tentative program for the General Sessions and Morning Lectures, and asked for any comment in person or by letter for improvement.

The Executive Secretary, Mr. Loveland, distributed an outline of the organization of the meeting and exhibits, and discussed the Boston arrangements for the Session. He reminded the Board that reservations at the headquarters' hotel had been made for all Officers, Regents and Governors of the College, and that there would be a dinner-meeting of the Governors and Regents at Boston on Sunday evening, April 20, for the general discussion of College affairs.

President Bruce announced meetings of the Credentials Committee at Philadelphia on March 23, 1941, and at Boston on April 20, 1941, and the next meeting of the Board of Regents at Boston on April 20, 1941, at 2:30 o'clock.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

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FACTORS INFLUENCING THE FATALITY RATE OF PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFONAMIDE COMPOUNDS *

By HARRISON F. FLIPPIN, M.D., F.A.C.P., LEON SCHWARTZ, M.D., and
JEFFERSON H. CLARK, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

THE introduction of sulfapyridine and sulfathiazole in the treatment of pneumococcic pneumonia constitutes the greatest advance in the control of this disease. Within the past three years numerous clinical reports have unquestionably established their therapeutic effectiveness, and the fatality rate of pneumococcic pneumonia has been markedly reduced with their use. Despite the proved value of this form of therapy, a certain percentage of pneumonia patients in whom these drugs are employed fail to recover. The purpose of this paper is to discuss the influence of several factors on the prognosis of this disease. This report is based on our experience with 800 adult pneumococcic pneumonia patients treated during the past two years with sulfapyridine or sulfathiazole. In this group of 800 patients there were 80 deaths (10 per cent mortality, table 1).

TABLE I
Results of Chemotherapy in 800 Typed Cases

Type	Number of Cases	Total Series		Negative Blood Cultures		Positive Blood Cultures	
		Incidence Per Cent	Mortality Per Cent	Number of Cases	Mortality Per Cent	Number of Cases	Mortality Per Cent
I	185	23.1	7.0	150	6.0	35	11.4
II	48	6.0	10.5	43	4.7	5	60.0
III	139	17.4	20.0	125	15.2	14	64.3
Others	428	53.5	8.0	386	4.7	42	38.1
Total	800		10.0	704	6.8	96	32.3

Age of Patient. As indicated in table 2, 54.2 per cent of our cases were 40 years of age or over. In the fatal series 83.7 per cent represented patients in this same age group. The mortality rate was 3.5 per cent for those patients 12 to 39 years of age, as compared to 15.4 per cent in the higher age group. This significant difference in mortality rates is largely a result of

* Received for publication December 20, 1940.

From the Committee for the Study of Pneumonia, Philadelphia General Hospital.
Aided by a grant from the American Philosophical Society.

the higher incidence of associated diseases in the older patients. In no other disease does youth, with the exception of the first year of life, prove as great an asset as in recovery from pneumonia. The age of the patient probably represents the most important single factor in the prognosis of this disease.

TABLE II
Influence of Age on Mortality

Age Group Years	Incidence Per Cent		Mortality Per Cent
	Total Series	Fatal Series	
12-19	10.5	1.3	1.2
20-29	16.9	5.0	2.2
30-39	18.4	10.0	5.5
40-49	22.3	23.7	10.6
50-59	15.3	27.4	18.0
60-69	10.8	17.6	16.4
70 and over	5.8	15.0	26.1
	45.8		3.5
	54.2		15.4
	83.7		

Time of Treatment. (Table 3.) In our entire series 65.3 per cent of the patients received treatment during the first four days of the disease with a mortality rate of 5.6 per cent, which represented 36.2 per cent of the fatal cases. Patients treated after the fourth day of illness (34.7 per cent) had a mortality rate of 18.4 per cent and constituted 63.8 per cent of the fatal series. Despite the effectiveness of chemotherapy, the length of time that elapses between the onset of the disease and the beginning of treatment has a definite bearing on prognosis. This is particularly so in patients treated after the fourth day of their illness.

TABLE III
Influence of Time of Treatment on Mortality

Day of Disease Treatment Started	Incidence Per Cent		Mortality Per Cent
	Total Series	Fatal Series	
1	4.5	2.5	5.5
2	18.1	11.2	6.2
3	24.6	15.0	6.3
	65.3		5.6
4	18.1	7.5	4.1
5	12.8	18.7	14.7
6	9.5	5.0	5.3
7	5.1	8.8	17.1
7+	7.3	31.3	43.1
	34.7		18.4
	63.8		

Type of Infection. As shown in table 1, the first three types of pneumococci responsible for the disease constitute 46.5 per cent of the cases. Not only are they the most prevalent, but they also give the highest mortality rate (12.2 per cent). This is a result of the high incidence (17.4 per cent) of Type III infections which resulted in a mortality rate of 20 per cent as compared to 7.0 and 10.5 per cent for Types I and II respectively. The high mortality rate in this sub-group is explainable on the high incidence of Type III infection in elderly and debilitated patients. From these data it is apparent that the type of pneumococcic pneumonia has a direct bearing on prognosis.

Bacteremia. The incidence of bacteremia in this group was 12 per cent (table 1), whereas in the fatal series, 40 per cent had positive blood stream

infections. The high fatality rate (32.3 per cent) for this group of bacteremic patients demonstrates the influence of this condition on the prognosis of pneumonia.

Complications. Complications of pneumonia developed in 48 (6.0 per cent, table 4) of our patients. In 35 (4.3 per cent) patients included in this sub-group, the complications were mild and none of the patients died. However, in the remaining 13 patients who developed severe complications, the mortality rate was 53.8 per cent. Although the incidence of serious complications is low (1.7 per cent), this factor has a definite bearing on the patient's chances of recovery.

TABLE IV
Influence of Complications on Mortality

Complications	Incidence Per Cent		Mortality Per Cent
	Total Series	Fatal Series	
Massive effusions.....	3.3	—	—
Empyema.....	1.3	5.0	40.0
Meningitis.....	0.3	2.5	100.0
Endocarditis.....	0.4	3.8	100.0
Otitis media.....	0.4	—	—
Metastatic abscess.....	0.1	—	—
Phlebitis.....	0.5	—	—
* Total.....	6.0	8.8	14.6

* Corrected for patients having more than one complication.

Associated Diseases. In this series of 800 patients, 264 (33 per cent, table 5) had other disease conditions in addition to pneumonia. The incidence of associated diseases was arrived at, in most instances, by selecting the outstanding condition present in each case. However, this was not always adhered to, as in seven patients suffering with acute alcoholism there

TABLE V
Influence of Associated Diseases on Mortality

Disease	Incidence Per Cent		Mortality Per Cent
	Total Series	Fatal Series	
Heart disease.....	11.3	35.0	31.1
Syphilis.....	7.3	8.8	12.1
Alcoholism.....	5.5	11.3	20.5
Asthma.....	2.0	1.3	6.3
Diabetes mellitus.....	3.0	3.8	12.5
Active pulmonary tuberculosis.....	0.8	2.5	33.3
Nephritis.....	3.5	5.0	14.3
Cerebral hemorrhage.....	0.4	3.8	100.0
Pregnancy.....	1.0	0.0	0.0
Carcinoma.....	0.2	1.3	100.0
* Total.....	33.0	70.8	20.1

* Corrected for patients in whom more than one associated disease has been listed.

was evidence of cardiac disease, and these were recorded in both sub-groups. Furthermore, in 58 patients the diagnosis of syphilis was based on positive serological findings alone, except in eight instances where there was evidence of cardiac involvement, and these were also recorded under heart disease. With the exception of these 15 patients (seven alcoholic, eight luetic) there

was no further duplication in our figures. Unsuspected diseases were found at necropsy in several patients. No doubt in other instances we failed to detect associated conditions, because in only 45 (56.2 per cent) of the fatal cases were postmortem studies performed. This same possibility exists for the non-fatal group. Heart disease not only represented the highest incidence of associated disease but also resulted in the highest fatality rate (31.1 per cent) with the exception of carcinoma, cerebral hemorrhage, and active pulmonary tuberculosis. In many of the cardiac patients the pulmonary infection was well under control and in several had entirely disappeared, but death occurred as a result of progressive cardiac decompensation or acute coronary occlusion. The relatively low incidence of alcoholism (5.5 per cent) in this report is a result of our hesitancy to make this diagnosis on history alone. However, those patients in whom this condition has been diagnosed represent cases of acute alcoholism. As indicated, the mortality rate (20.0 per cent) for this sub-group is twice that of the entire series (10.0 per cent). The presence of pregnancy in eight patients without a death is of interest, in view of the expected high fatality rate of this condition prior to sulfonamide therapy. From these data it is apparent that the presence of certain associated diseases has a significant bearing on the prognosis of pneumonia. No doubt many of these patients suffering with pre-existing conditions would still be alive if pneumonia had not developed. However, the mere presence of many of these diseases results in a high incidence of pulmonary infections, such as pneumonia.

Race and Sex. It has been claimed that the race and sex of patients suffering with pneumonia have an influence on prognosis. In our experience (table 6) these factors appear to be of little or no significance.

TABLE VI
Influence of Race and Sex on Mortality

Race	Sex	Incidence Per Cent		Mortality Per Cent
		Total Series	Fatal Series	
White	Male	45.3	46.2	10.2
	Female	27.1	25.0	9.2
Colored	Male	17.2	21.3	12.4
	Female	10.4	7.5	7.2

Place of Treatment. All of the patients referred to in this report are hospital treated cases. However, a word should be said regarding the comparative fatality rates of patients cared for at home, and in those who are hospitalized for treatment. With the widespread distribution and use of the sulfonamide drugs, more patients are being treated at home. Those in whom drug therapy has apparently failed at home are often sent to a hospital, and these usually represent seriously ill pneumonia cases. It is, therefore, apparent that more patients will probably now recover from

pneumonia than previously, although the mortality rate for this disease in hospitals may become increasingly higher.

Drug Toxicity. Because of certain toxic effects associated with the administration of these drugs, their use in pneumonia is sometimes prevented. If it is impossible to employ chemotherapy because of one of these untoward toxic manifestations, the patient's chances of recovery are reduced unless type specific serum is available. Furthermore, if certain of these toxic effects are overlooked, and the use of the drug is continued, it may lead to a more serious condition than that caused by the infection. Although we have observed several patients in whom drug toxicity necessitated stopping chemotherapy, there were no deaths attributable to the drug. In several instances it was necessary to administer type specific serum after discontinuing the drug. With the continued use of these compounds in many types of infections it is possible that more individuals will develop drug sensitivities, and the problem of the toxic effects of chemotherapy may become more acute in the future.

Other Factors. The patient's geographic location, as well as the fact of his living in a rural or urban community, influences the incidence and probably the prognosis of pneumonia. This report deals entirely with patients living in the city of Philadelphia, where, until recently, the expected mortality from this disease was 25 to 35 per cent. Of considerable importance is the economic status of the patient. Certainly we should expect a higher fatality rate in those who are inadequately sheltered, have occupations that expose them to cold and dampness, have poorly balanced diets, and possess unsuspected or untreated diseases. Furthermore, in some, because of financial reasons, or of slow mental activity, the seeking of medical aid is deferred until the patient's condition becomes alarming. The majority of our patients are from a low income class, and many are dependent on aid from relief agencies. Over-indulgence in alcohol, as shown in table 5, decreases the patient's chances of recovery; and also, because of the habits associated with alcoholism, the incidence of the disease is increased.

DISCUSSION

Whether the mortality rate of 10 per cent, as reported in this paper for hospital treated cases, will be further reduced is a matter for conjecture. There is little reason to believe that the future will influence the incidence of the more severe types of infecting organism, the incidence of bacteremia, the age of the patient, the number of associated diseases, or the occurrence of alcoholism (table 7). However, we may, through widespread lay education, influence the number of patients who are treated during the first four days of their illness. If this is achieved we may expect a reduction both in the incidence of serious complications and in mortality rate from pneumonia. On this hangs the most important single factor in the future control of this disease. No doubt further experience will result in a better understanding and more intelligent use of these drugs and serum in the

future and this may decrease the present fatality rate. However, the widespread distribution and administration of sulfonamide therapy in pneumonia will have a definite influence on hospital practice. More of our cases will be treated at home, and only the severe ones will be sent to a hospital.

TABLE VII
Summary of Significant Factors Influencing Mortality Rate

Factors	Incidence Per Cent		Mortality Per Cent 10.0%
	Total Series 800 Cases	Fatal Series 80 Cases	
Age..... 12-39	45.8	16.3	3.5
Years..... over 39	54.2	83.7	15.4
Type of infection ... I and II	29.1	22.5	7.7
III	17.4	33.8	20.0
Others	53.5	43.7	8.1
Bacteremia	12.0	40.0	32.3
Day of disease 1-4	65.3	36.2	5.6
Treatment started .. over 4	34.7	63.8	18.4
Complications	6.0	8.8	14.6
Associated diseases ..	33.0	70.8	20.1

This will undoubtedly result in a reduction in the general mortality, but the fatality rates in hospital treated cases will not be reduced. In fact, it is our impression that in the future we may expect even higher mortality rates from hospitals than those that have been reported during the past several years.^{1, 2, 3, 4, 5, 6}

SUMMARY

1. Eight hundred pneumococcic pneumonia patients are presented, in whom sulfonamide therapy was employed. There were 80 deaths.

2. The influence of certain factors on the prognosis of the disease is discussed.

3. The future with respect to the fatality rate of pneumonia is considered.

We wish to express our thanks to John J. Shaw, M.D., Secretary of Health, Commonwealth of Pennsylvania, for his interest and help in this and related studies on pneumonia.

REFERENCES

1. EVANS, G. M., and GAISFORD, W. F.: Treatment of pneumonia with 2-p (aminobenzene-sulfonamido) pyridine, *Lancet*, 1938, ii, 14.
2. FLIPPIN, H. F., LOCKWOOD, J. S., PEPPER, D. S., and SCHWARTZ, L.: Treatment of pneumococcic pneumonia with sulfapyridine, *Jr. Am. Med. Assoc.*, 1939, cxii, 529.
3. PLUMMER, N., and ENSWORTH, H. K.: Sulfapyridine in the treatment of pneumonia, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1854.
4. SCHWARTZ, L., FLIPPIN, H. F., and TURNBULL, W. G.: The treatment of pneumococcic pneumonia: a comparative study of 351 patients treated at the Philadelphia General Hospital, *ANN. INT. MED.*, 1939, xiii, 1005.
5. FLIPPIN, H. F., SCHWARTZ, L., and ROSE, S. B.: The comparative effectiveness and toxicity of sulfathiazole and sulfapyridine in pneumococcic pneumonia, *ANN. INT. MED.*, 1940, xiii, 2038.
6. FLIPPIN, H. F., REINHOLD, J. G., and SCHWARTZ, L.: Sulfapyridine and sulfathiazole therapy in pneumococcic pneumonia, *Jr. Am. Med. Assoc.*, 1941, cxvi, 683.

THREE CASES OF ACUTE SYPHILITIC NEPHROSIS IN ADULTS *

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THREE patients with acute syphilis have been seen in this clinic during the past two years who exhibited the picture of nephrosis and whose course justified a diagnosis of acute syphilitic nephrosis. Since there are few reports of similar cases in the literature, one is led to conclude that this is a rare complication of early syphilis. In 1935 Hermann and Marr¹ reviewed the literature on clinical syphilitic nephropathies and devised a classification of these conditions. They found nine cases which were considered characteristic of acute syphilitic nephrosis. Since Hermann and Marr's contribution, there have been no other reported cases of typical acute syphilitic nephrosis in the literature available to us. Baker² recently published an excellent case study of a 25 year old male with evidence of secondary syphilis and a nephrotic renal syndrome. But in this case the clinical picture was confused by the presence of an enlarged heart which rapidly returned to normal size as the patient improved. Because of the circulatory abnormality it is impossible to regard this as an instance of acute syphilitic nephrosis. Of the reported cases less than half have come from the United States. Only one is from the southeastern United States where the incidence of syphilis is generally considered the highest in this country.

According to Hermann and Marr acute syphilitic nephrosis is characterized by an abrupt onset of the nephrotic syndrome in patients who are in the late primary or secondary stage of syphilis. Typical features include massive edema and albuminuria, low total blood serum proteins with particular depletion of the albumin fraction, oliguria, elevated blood cholesterol, lowered basal metabolic rate, a strongly positive complement fixation test for syphilis and, finally, prompt recovery following anti-syphilitic treatment. Frequently doubly refractile lipid bodies are found in the urinary sediment. Significant elevation of the blood pressure, eye ground changes, impairment of renal function, hematuria and cylindruria are usually absent. These abnormalities characterize a syndrome which differs significantly from the other clinical types of syphilitic nephropathies, namely simple syphilitic albuminuria and subacute and chronic syphilitic nephrosis. However, the latter types seem closely related to the syndrome of acute syphilitic nephrosis and are distinguished from it principally by evidence of less renal and systemic involvement in the case of simple albuminuria and by the differences in time of onset, chronicity and response to specific therapy in the subacute and chronic nephrotic types.

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The three cases from the Vanderbilt University Hospital satisfy most of the criteria proposed by Hermann and Marr for acute syphilitic nephrosis, and are reported below:

CASE REPORTS

Case 1. J. S., a 57-year-old white man, developed an acute urethral discharge six weeks before admission to the Vanderbilt University Hospital. This was treated elsewhere without improvement and at the time of his first visit he exhibited a purulent urethral discharge and a generalized macular rash involving the palms and the soles. The blood Wassermann and Kahn tests were positive. The patient was given two injections of neoarsphenamine which were separated by an interval of three days and consisted of 0.6 gm. each. Twenty-four hours after the second injection he noted oliguria and edema of the ankles. The edema became progressively worse until the time of admission four days later.

The past history revealed several episodes of acute urethral infection, presumably gonorrhea, but nothing suggestive of nephritis. There was no history of previous syphilitic infection and the blood Wassermann and Kahn tests were said to have been negative five years before the present illness.

Physical Examination: The patient did not appear acutely ill. He exhibited a fading diffuse macular rash which involved the soles and palms. There was a general glandular enlargement. The eye-lids were not edematous and the ophthalmoscopic findings were normal. The peripheral vessels were not remarkable. The blood pressure was 136 mm. of Hg systolic and 80 diastolic. The heart and lungs were normal. No abdominal viscera were palpably enlarged. There was a purulent urethral discharge and a severe balanitis. The prostate was enlarged, tender and boggy. Both lower extremities were quite edematous. The reflexes were normal.

Laboratory Findings: The specific gravity of the urine was 1.030; albumin ("4 plus") was present and there were many hyaline and granular casts and occasional white and red blood cells in the centrifuged sediment. No doubly refractile bodies were observed in the urine. He excreted 75 per cent of phenolsulphonphthalein in a two hour period. The non-protein nitrogen of the blood was 26 mg. per 100 c.c.; cholesterol 333; total serum proteins 5.30 gm. per 100 c.c.; serum albumin 2.51; serum globulin 2.79. The Wassermann and Kahn tests on the blood were strongly positive. The red blood cell count was 4.3 million per cu. mm.; white blood cell count, 10,000; hemoglobin 12 grams per 100 c.c. The differential leukocyte count was normal. A stool examination revealed no blood or parasites. The basal metabolic rate was +4 per cent.

Course: A high protein, salt poor diet was prescribed and fluids were restricted to 2000 c.c. in 24 hours. He was confined to bed. On this regimen he continued to excrete in the urine approximately 15 gm. of albumin daily and no change occurred in the urinary sediment. Six days after admission he was given 0.1 gm. and three days later 0.2 gm. of neoarsphenamine. Three days after the second injection the amount of albumin in the urine fell abruptly to 2 grams in 24 hours. Subsequently the albuminuria rapidly disappeared. Within nine days after the first treatment with neoarsphenamine the total serum proteins had risen to 6.05 gm. per 100 c.c. of blood, the albumin to 3.33 and the globulin fraction was essentially unchanged.

The patient was discharged from the hospital free of symptoms. Anti-syphilitic treatment was continued in the out-patient Syphilis Clinic where he has been followed regularly for the past two years. During this period he has completed the prescribed courses of treatment. The Wassermann and Kahn tests on the blood have become negative and the cerebrospinal fluid is normal. The blood pressure has remained normal and at no time has he complained of urinary tract symptoms. Repeated ex-

aminations of the urine have revealed normal values for specific gravity, occasional faint traces of albumin, and rare white blood cells in the centrifuged sediment. No red blood cells or casts have been observed. The non-protein nitrogen, total serum proteins and albumin-globulin ratio of the blood have remained normal.

Case 2. L. M. B., a negress aged 22, was admitted to the hospital complaining of backache and edema about the eyes. Two weeks before admission she noted the onset of dull pain in the lumbar region. One week later mild dysuria and frequency occurred. This was followed in two days by the development of puffiness of the eyelids. She denied the occurrence of manifestations of early syphilis.

Her past history was essentially negative. She had always experienced excellent health and there was nothing in the history suggestive of a previous attack of acute nephritis. She had noted chronic vaginal discharge for five years. Four months before the present illness Wassermann and Kahn tests on the blood were negative. These examinations were made in the laboratories of this hospital.

Physical Examination: She exhibited moderate edema of her eyelids but otherwise appeared quite well. There were numerous pigmented scars over the face and back. There was no general glandular enlargement but one large, firm, discrete gland was present in the left inguinal region. The retinae were very pale but were normal otherwise. There were no mucous patches in her mouth. The lungs were not remarkable and the heart was normal except for a systolic murmur heard best at the pulmonic area. The retinal and peripheral vessels were not abnormal. The blood pressure was 130 mm. of Hg systolic and 76 diastolic. No abdominal viscera were palpable. On the left labium majorum there was a healed scar, slightly elevated, about 2 cm. in diameter. The pelvic examination revealed chronic endocervicitis with moderate purulent discharge. Minimal pretibial edema was present. The reflexes were normal.

Laboratory Findings: A catheterized specimen of urine contained a huge amount of albumin ("4 plus"). The specific gravity was 1.018 and the reaction acid. The urine contained numerous hyaline casts but no red blood cells or white blood cells. Doubly refractile bodies were not observed. A culture of the urine yielded no growth. Blood studies revealed a hypochromic microcytic anemia; red blood cell count, 4.49 million; white blood count, 7,800; hemoglobin 7.8 gm. per 100 c.c. of blood. The differential white blood cell count was normal. The Wassermann and Kahn tests on the blood were positive. The total serum protein of the blood was 5.72 gm. per 100 c.c.; albumin 2.44 and globulin 3.28. The non-protein nitrogen of the blood was 29 mg. per 100 c.c.; cholesterol, 250; blood chlorides, 577. The patient excreted 50 per cent of phenolsulphonphthalein in one hour. The basal metabolic rate was minus 2 and minus 12 on successive days. Cervical smears revealed intracellular gram negative diplococci. Darkfield examinations of fluid obtained from the inguinal lymph node and from the healed scar were positive for *Treponema pallida*. No spirochetes were observed in repeated darkfield examinations of the urine centrifugate. A specimen of urine centrifugate was injected into the testicle of a rabbit. The rabbit did not develop syphilis.

Course: Bed rest and a high protein, low salt diet were prescribed. Fluids were limited to 1400 c.c. in 24 hours. During the first three days the output of urine ranged between 700 and 1100 c.c. with persistent albuminuria ("four plus"). Spontaneous diuresis then occurred. The patient excreted from 2000 to 2600 c.c. of urine daily for four days. This was associated with a rapid decline in the amount of albumin, which after the fourth day entirely disappeared. The output of urine then diminished to approximately 1000 c.c. daily. The low total serum protein and the reversed albumin-globulin ratio persisted. Neoarsphenamine (0.3 gm.) was given on the twelfth hospital day. Four days later a second injection, 0.45, was administered. Nine days after instituting specific therapy the serum albumin rose to 4.10 while the globulin remained at 3.21 gm. per 100 c.c.

Throughout the period of hospital observation the patient's blood pressure, temperature, and pulse remained normal. Following the administration of iron, the hemoglobin rose rapidly to a normal level and the patient was discharged free of symptoms. Anti-syphilitic treatment was continued in the Out-Patient Department.

Twenty months after treatment was instituted the urine contained no albumin. The specific gravity of a single specimen was 1.026. The non-protein nitrogen of the blood was 31 mg. per 100 c.c.; the total serum proteins, 6.54 gm.; the albumin-globulin ratio normal. During the period of anti-syphilitic treatment she experienced no symptoms of kidney disease and her blood pressure remained normal. Under treatment the Wassermann and Kahn tests became negative and the cerebrospinal fluid proved to be entirely normal.

Case 3. A. M. M., a negress aged 19, considered herself perfectly well until three weeks before admission to this hospital. At this time she noted an enlarged non-tender inguinal lymph node. One week later she developed a generalized cutaneous rash and a non-tender swelling of her left labium majorum. During the ensuing two weeks she experienced gradually increasing discomfort on urination at the site of this labial lesion.

As a child she had several severe sore throats but never any symptoms suggesting nephritis. Otherwise she gave no history of any previous illness. During her only pregnancy, one year before the present illness, she experienced no frank toxic symptoms.

No history of a primary syphilitic lesion could be obtained.

Physical Examination: The patient appeared quite comfortable. There was definite swelling of the soft tissues about the eyes and slight pitting edema of the forehead. A maculopapular rash was distributed irregularly over the extremities and trunk. The lymph nodes were generally and discretely enlarged. The mucous membranes were slightly pale. No mucous patches were observed. The retinal and peripheral vessels appeared normal and no retinal hemorrhages or exudates were present. The blood pressure was 90 mm. Hg systolic and 50 diastolic. There was a faint systolic murmur at the pulmonic area but otherwise the heart and lungs were entirely normal. No abdominal viscera were palpably enlarged. The left labium was markedly swollen and slightly indurated. Both labia exhibited excoriated areas. There was slight pitting edema of the lower extremities. The reflexes were normal.

Laboratory Findings: On admission a catheterized urine specimen revealed albuminuria ("4 plus"), occasional white blood cells, no red blood cells and rare granular casts. No doubly refractile bodies were seen in the urine. She excreted 45 per cent of phenolsulphonphthalein in the first hour and 15 per cent in the second hour. On a Fishberg test regimen she attained a maximum urinary concentration of 1.032. The non-protein nitrogen of the blood was 21 mg. per 100 c.c.; cholesterol 151; icteric index 1.5; sodium chloride 561; total serum proteins 5.95 gm. per 100 c.c.; serum albumin 2.80; serum globulin 3.15. The Wassermann and Kahn tests on the blood were strongly positive. The red blood cell count was 4.73 million per cu. mm.; white blood cell count, 6000; hemoglobin, 9 grams per 100 c.c. The differential leukocyte count was normal. A roentgen-ray examination of the chest and an electrocardiogram revealed no abnormalities. A catheterized urine specimen was centrifuged promptly and the centrifugate examined by the darkfield method. No *Treponema pallida* were seen. The centrifugate was injected into a rabbit's testicle. No syphilitic lesion developed. Darkfield examinations of the serum from the vulval lesion were positive for *Treponema pallida*.

Course: The patient was given an unrestricted diet and the fluid intake was not limited. Heavy albuminuria persisted for two days after the initial examination, and then abruptly decreased to only a trace. Subsequently she was given a blood serum transfusion of 100 c.c. and a whole blood transfusion of 500 c.c. She was given an

uninterrupted fever treatment at which time her rectal temperature was maintained at 41.5° Centigrade for 15 hours. She bore this treatment well but the urine continued to contain a faint trace of albumin for three days. Two days after artificial hyperpyrexia the blood non-protein nitrogen was 23 mg. per 100 c.c. of blood but there was no increase in the serum albumin value over the admission determination. Five days after fever therapy *Treponema pallida* were found on darkfield examination of serum from the vulval lesion.

No arsenical therapy was given this patient for a period of four weeks after therapeutic hyperpyrexia. During this period albuminuria entirely disappeared. She then experienced a recurrence of syphilitic skin lesions. Albuminuria did not recur. At the time of the cutaneous relapse the blood non-protein nitrogen was 24 mg. per 100 c.c. and the total serum proteins were 6.00 gm. per 100 c.c. of blood with an albumin value of 4.20 gm. Treatment with arsphenamine was then instituted. She has received four doses, 0.3 gm. each, of arsphenamine without untoward reactions.

DISCUSSION

The pathology of acute syphilitic nephrosis is quite obscure. Post-mortem studies have been made only on subjects who had been exposed during life to poisoning from arsphenamine or mercury. Warthin³ described tubular changes in the kidneys in a case of secondary syphilis and albuminuria. However, arsphenamine poisoning was the cause of death and doubtless complicated the renal findings. Dieulafoy⁴ described similar renal changes but in this instance mercury had been employed therapeutically.

In the absence of satisfactory pathological studies it has been postulated that the passage of spirochetes through the renal tubules may be the cause of the nephrosis. Vorpahl,⁵ Hoffman,⁶ and Fiessinger and Huber⁷ have reported the presence of *Treponema pallida* in the urine of syphilitic patients. Warthin subsequently recorded the demonstration of spirochetes passing into the renal tubules of several subjects who had had acute syphilis. These reports have been subjected to much criticism both as regards the specific nature of the spirochetes and the accuracy of the clinical diagnoses.

No attempts to demonstrate the presence of spirochetes in the urine by animal inoculation have been reported previously. This was done in two of our cases. The centrifugates of urine obtained by catheterization were injected into the testicles of rabbits. No syphilitic lesions developed. The collection, centrifugation and injection of the specimens were carried out rapidly. The negative results in two typical cases of syphilitic nephrosis cast considerable doubt upon the hypothesis that the passage of spirochetes through the tubules is an important factor in the pathogenesis of acute syphilitic nephrosis.

Two injections of neoarsphenamine, separated by an interval of three days and consisting of 0.6 gm. each, were given to the first patient and the onset of nephrosis occurred one day after the second treatment. It seems extremely unlikely that arsenic caused the nephropathy since the latter disappeared while the patient was receiving additional treatment with neoarsphenamine. The rapidity with which the nephropathy disappeared

following the reinstitution of treatment was impressive. However, no treatment factor operated in cases 2 and 3, since the development of the nephropathy antedated the institution of specific therapy. Moreover, spontaneous remission of symptoms and signs without benefit of anti-syphilitic treatment occurred in these cases. This has not been recorded heretofore in acute syphilitic nephrosis. In the light of the observation that spontaneous remissions do occur it appears reasonable to assume that the nephrotic syndrome may develop and undergo spontaneous remission without recognition by either patient or physician.

SUMMARY

1. Three cases of acute syphilitic nephrosis are reported.
2. In two cases unsuccessful efforts were made to demonstrate *Treponema pallida* by inoculating rabbits intratesticularly with urine centrifugates.
3. In two cases the nephrotic syndrome underwent spontaneous remission without benefit of antisyphilitic treatment.

BIBLIOGRAPHY

1. HERMANN, G., and MARR, W. L.: Clinical syphilitic nephropathies, Am. Jr. Syph. and Neurol., 1935, xix, 1-29.
2. BAKER, B. M., JR.: The relation of syphilis to nephritis, Bull. Johns Hopkins Hosp., 1939, lxxv, 196-211.
3. WARTHIN, A. S.: The excretion of *Spirocheta pallida* through the kidneys, Jr. Infect. Dis., 1922, xxx, 569-591.
4. DIEULAFOY, GEORGES: Clinique médicale de l'Hôtel Dieu de Paris, 1899, Mason et Cie, Paris, ii, 242.
5. VORPAHL, K.: Spirochätenbefund im Urin bei Nephritis syphilitica, München. med. Wchnschr., 1912, lix, 2811-2813.
6. HOFFMAN, E.: Ueber akute syphilitische Nierenentzündung in der Frühperiode, Deutsch. med. Wchnschr., 1913, xxxix, 253-256.
7. FIESSINGER, N., and HUBER, J.: Un cas de Treponemurie au cours de la syphilis secondaire, Bull. et mem. Soc. med. d'hôp. de Paris, 1921, xlv, 146-150.

THE HORMONAL, CENTRAL AND RENAL ORIGIN OF "ESSENTIAL" HYPERTENSION (CEREBRAL AND RENAL ARTERIOSCLEROTIC ISCHEMIA AS CAUSAL FACTORS) *

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EXPERIMENTAL FACTS

THERE exist several experimental methods of producing persistent arterial hypertension: (1) section of the cardio-aortic and carotid sinus "moderator nerves" ¹⁻³; (2) impairment of the cerebral blood flow through either intracranial injection of kaolin suspension ⁴ or ligation of most of the vessels which supply the brain circulation ⁵; (3) impairment of the renal blood flow ^{6, 7}; (4) repeated intramuscular injections of "hypertonin," which is obtained through ultra-filtration of the serum of hypertensive patients, ⁸ and of various hormonal sterols. ¹⁸⁵

Elevation of blood pressure following section of the moderator nerves, although a phenomenon of outstanding theoretical interest, apparently has no bearing upon the problem of arterial hypertension in man, as there are neither anatomical ^{9, 145, 146} nor clinical ^{147, 148, 149} signs of an alteration of the moderator nerve system in clinical arterial hypertension.

Artificial Central Hypertension. Artificial impairment of the cerebral blood supply as produced through intracranial kaolin injections ⁴ or ligation of the brain vessels ⁵ causes local shortage of oxygen. Shortage of oxygen is followed by an accumulation of unoxidized lactic acid and other metabolites in the brain tissue, ^{141, 142, 143, 144} and lactic acid not only stimulates the cerebro-medullary vasoconstrictor centers but also increases their reactivity to various other kinds of stimuli. ^{10, 24} Both the pressor effect of stimulation of peripheral nerves and of CO₂ inhalation and the depressant effect of loss of CO₂ through hyperventilation are intensified during perfusion of the brain stem with blood containing added amounts of lactic acid ¹⁰ (see table 1). Analogous conditions are usually found in clinical "essential" hypertension. The stimulating and sensitizing effect of cerebral ischemia upon the vasoconstrictor centers has been fully confirmed by Heymans ¹⁵³ and Heymans, Nowak and Samaan. ¹⁵⁴ Gellhorn and Lambert ¹⁶⁶ also have recently repeated and confirmed the experiments of Raab ¹⁰ concerning the increased vasomotor irritability due to shortage of oxygen. However, the claim of these authors that this phenomenon is not of a central nature is incompatible with well established facts and evidently based upon the misleading effects of anesthesia in their experiments.

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Artificial Renal Hypertension. The mechanism of arterial hypertension during artificial impairment of the renal blood supply^{6, 7, 25, 26} does not seem to be of a primarily nervous nature as it occurs also after denervation of the kidneys,²⁷ after sympathectomy,²⁸ after destruction of the spinal cord,¹⁸⁶ and even if the kidneys are entirely isolated and connected with the body only through cannulas.²⁹ However, its abolition by pithing¹⁶⁷ suggests some participation of the central vasomotor apparatus.

TABLE I
Experiments on Decerebrate Cats (Raab¹⁰)

	No. of Experiments	Average Reaction of Systolic Blood Pressure in mm. Hg
CO ₂ inhalation normal	7	+27
CO ₂ inhalation during shortage of O ₂	7	+46
CO ₂ inhalation normal	9	+26
CO ₂ inhalation during perfusion of brain stem with lactic acid	9	+48
CO ₂ inhalation normal	6	+18
CO ₂ inhalation after injection of lactic acid into sub-occipital cavity	6	+46
Hyperventilation normal	9	+ 7
Hyperventilation during perfusion of brain stem with lactic acid	9	-23
Faradisation of crural nerve normal	9	+24
Faradisation of crural nerve during perfusion of brain stem with lactic acid	9	+49

Opinions concerning the rôle of the suprarenal glands in experimental renal hypertension are contradictory. Some authors^{25, 30} consider it as essential, others^{31, 32, 33, 152} do not. Formation of vasopressor substances within the ischemic kidney tissue itself has been made probable by various authors.^{34, 35, 36} Cortical hormones of the suprarenal glands are believed to intensify their effect.¹⁶² Normal kidney tissue has been found to contain blood pressure lowering substances both with acute¹⁷⁶ and with slow and prolonged action.^{177, 178, 179} According to recent investigations¹⁸⁰ the "hypertension mediator" substance seems to be destroyed by normal metabolic activity of the kidneys. Tyrosinase counteracts artificial renal hypertension.¹⁸⁸

A participation of humoral (renal?) factors both in the centrogenous "kaolin hypertension" and in its abolition through denervation of the kidneys³⁷ is suggested by the effects of transfused blood of such experimental animals.¹⁷³

Artificial Hormonal Hypertension. Westphal and Sievert⁸ succeeded in producing prolonged elevations of blood pressure by injecting "hypertonin," a supposedly hormonal substance which they had isolated from the serum of hypertensive patients. It increases the size of the suprarenal glands and is

effective only in their presence. Its blood pressure-elevating effect is enhanced by cholesterol.

Vasopressin from the posterior pituitary lobe, if injected into the suboccipital cavity, raises the blood pressure for a few hours,^{38, 39, 40} probably through cerebral vasoconstriction and local ischemia.¹⁷⁴ Anterior lobe preparations are ineffective.⁴⁰ The presence of the pituitary gland does not seem to be indispensable for the production of experimental renal hypertension,³² although the latter is diminished after hypophysectomy.⁴¹

Various purified hormonal sterols, such as desoxycorticosterone, estradiol, progesterone and testosterone were found to produce hypertension in rats, supposedly due to "renal injury."¹⁶⁵ Also in human individuals hypertension was brought about by the administration of desoxycorticosterone acetate.¹⁸³

Compounds of cortical lipoids and adrenalin exert an intensifying effect upon the development of experimental arteriosclerosis²³ (see figure 1) and



FIG. 1. Atheromatosis (cholesterol deposits) in the intima of rabbit's aorta after 35 days' preparatory treatment with suprarenal extract (288 mg. lipoid-adrenalin compound) and subsequent cholesterol feeding (7 gm. in 14 days). In untreated animals it takes at least two months' cholesterol feeding to produce this effect. (Raab.²³)

act as peripheral vasoconstrictors.^{42, 43} Sterols of probably adreno-cortical origin have been found by the author to be present in the tissue of arterial walls.¹⁸² Abnormally large amounts were observed in the arteries of a case of cortical adenoma. The degree of sensitization of the blood vessels to the vasoconstrictor effect of renin¹⁶² may depend partly upon the composition and concentration of these hormones in their muscular tissue. Adrenalin itself can also be formed in the adrenergic neurons of the arteries⁴⁴ and its vasopressor effect is enhanced by the presence of cortical sterols (figure 2).^{181, 187}

Vogt⁴³ observed an increase of vasopressor substances of supposedly suprarenal origin in the blood in centrogenous "kaolin hypertension."⁴ However, the presence of the suprarenal glands is not indispensable for the production of this type of hypertension.^{184, 185}

According to Steinach, Peczenik and Kun⁴⁵ the cerebral circulation decreases after castration but is restored to normal through the administration of sex hormones. The authors consider this phenomenon as important for both the pathogenesis and therapy of arterial hypertension.

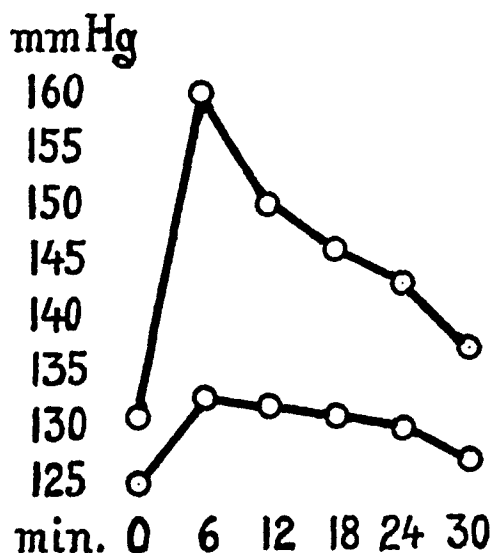


FIG. 2. Intensification of the blood pressure effect of adrenalin (0.5 mg.) through pre-treatment with desoxycorticosterone acetate (Cortate Schering, 110-150 mg. within 4 to 6 days). Average of 6 experiments. Lower curve before, upper curve after administration of Cortate.

MORPHOLOGICAL FACTS

Central Changes. The existence of purely central forms of arterial hypertension in man has been demonstrated with certainty in those rather rare instances where hypertension developed suddenly with the onset of bulbar poliomyelitis^{46, 47} or encephalitis,¹⁴⁰ after concussion of the brain^{22, 48, 49} or after CO-poisoning,^{50, 51} and where anatomical changes were found in the areas of the vasoconstrictor centers. However, these forms do not belong in the group of "essential" hypertension.

Arteriosclerotic changes which suggest the occurrence of local ischemia were found by Bordley and Baker⁵² in the medulla oblongata of patients with essential hypertension. Cutler⁵³ and Tuthill⁵⁴ confirmed these findings in only about 50 per cent of their autopsied hypertensive cases, but Cutler emphasizes that, if present, they were always accompanied by arterial hypertension. Severe arteriosclerotic changes of the smallest vessels of the brain-stem of hypertensives have been described by Rühl,⁵⁵ and by Büchner and Wirtz.⁵⁶ The latter observed destructive changes of the brain-stem ganglia (of the same type as artificially produced through shortage of oxygen) in all cases of hypertension, even in young individuals. Trophic lesions of the brain-stem ganglia of the ischemic type have been found in essential hypertension also without visible anatomical changes of the brain vessels.^{57, 58} They

are to be ascribed either to functional cerebrovascular spasms or to chemical alterations of the vascular walls which escape microscopic detection. This is the case, for instance, regarding small cholesterol deposits in the arterial walls which can be discovered only through chemical analysis⁵⁹ but may suffice to impair the gaseous exchange between blood and brain cells.⁶⁰ Plasma exudation around the small brain vessels, as is found in hypertensive cases, seems to have a similar detrimental effect upon the cerebral cellular oxygen supply.⁶¹ Thus, shortage of oxygen within the cerebro-medullary vasoconstrictor centers and its blood pressure elevating effect may be caused both by a diminution of vascular blood supply and by impairment of oxygen penetration into the cells of the centers.

An increasing lipid infiltration and hyalinization of the smallest vessel walls and a gradual diminution of cerebral blood flow have been found to be common features of advancing age even in the absence of distinct atheromatosis of the larger brain vessels.^{58, 62, 63, 64, 65, 66, 151} This fact is usually overlooked at routine autopsies. The brain tissue requires eight to ten times more oxygen than an equal volume of muscular tissue,⁵⁷ and even slight alterations of the cerebro-medullary blood supply will probably not remain without functional consequences on the part of the vasomotor centers. It is true that cerebral sclerosis in general is not always accompanied by arterial hypertension. The occurrence or absence of the latter will depend upon the local distribution of vascular changes in those widespread areas of brain-stem and medulla oblongata where vasoconstrictor (and vasodilator?) centers are scattered, and also upon some factors of peripheral nature (condition of the heart, of the suprarenal glands, etc.). Gross arteriosclerotic changes of the brain were recorded in the necropsy findings of 87 per cent of 131 cases of arterial hypertension and in 41 per cent of 83 non-hypertensive mostly senile cases in some Vienna hospitals.¹⁶ Statements concerning the much more important smaller cerebro-medullary vessels were lacking throughout, as is usual in routine autopsy records.

Many authors have described cases of arterial hypertension with considerable arteriosclerosis of the brain but no vascular changes within the kidneys.^{52, 67, 68, 69, 70, 71, 72, 150, 156} In cases like these the origin of the hypertension consists obviously in the stimulating and sensitizing effect of local ischemic asphyxia upon the vasoconstrictor cerebro-medullary centers. It was Riebold's⁶⁷ merit to have established this fact in 1917 in a paper entitled "Permanent considerable arterial hypertension as an early symptom of cerebral arteriosclerosis."

Renal Changes. So-called "essential" hypertension, according to the original terminology, is characterized by the absence of clinically detectable signs of renal involvement, but there cannot be any doubt that in a great number of cases analogous vascular lesions to those in the brain are also, or even exclusively, present in the kidneys.^{71, 73} Very often they do not manifest themselves clinically; nevertheless, their concealed presence may account

for marked elevation of blood pressure in accordance with the experimental findings of Hartwich,⁶ Goldblatt,²⁵ Enger, Linder and Sarre,²⁶ etc. However, absence of high blood pressure has repeatedly been noted in spite of renal arteriolosclerosis.^{74, 75, 76} The mode of production of vasopressor substances in the ischemic kidney is not yet clear, but there is some evidence that certain granulated cells in the walls of the juxtaglomerular portion of the afferent arterioles may be considered as their place of origin.^{163, 164}

TABLE II

Arteriosclerosis and Gross Suprarenal Changes in Primary Hypophyseal Disturbances

Pituitary Disturbances	No. of Cases	Average Age Years	No. of Cases with Arteriosclerosis (% of Total No.)	Degree of Arteriosclerosis (% of Total No.)			Suprarenals (% of Total No.)*		
				-	+	++	Apparently normal	Enlarged	Atrophic
Anterior lobe basophilism and acromegaly	59	47	92	8	11	81	37	63	0
Adiposogenital dystrophy and hypophyseal cachexia	34	44	44	56	27	17	42	9	49

These figures were calculated from autopsy records which A. Ruggieri has collected in Vienna hospitals and from the literature. They give a rough impression of the relationship between pituitary hyper- and hypofunction with the condition of the suprarenal glands and the development of arteriosclerosis.

* The total number of findings concerning the suprarenals was 37 in the first and 27 in the second group.

The rather frequent complete absence of renal vascular changes in essential hypertension invalidates the view of some authors that renal ischemia is the sole cause of this disease. In addition to numerous other observations of permanent hypertension *without* vascular changes of the kidneys Fahr¹⁵⁰ has recently published 44 such cases which had been autopsied within a period of only two and a half years. Again in most of them macroscopically visible cerebral arteriosclerosis was recorded.

TABLE III

Reaction of Blood Pressure to Changes in the Alveolar CO₂ (Raab^{16, 170})

	Type of Cases	No. of Experiments	Average Level of Blood Pressure mm. Hg	Average Reaction of Blood Pressure mm. Hg
Inhalation of CO ₂	Acute glomerulonephritis	12	140	+ 6
	"Essential" and nephrosclerotic hypertension	40	178	+34
Hyperventilation	Normals	15	100	± 0
	Acute glomerulonephritis	6	163	± 0
	"Essential" and nephrosclerotic hypertension	40	198	-30

Changes of Endocrine Glands. The most outstanding anatomical changes of the endocrine system which are usually accompanied by arterial hypertension are basophile adenomata of the anterior pituitary and tumors of the suprarenal glands, both cortical and medullary.^{23, 158, 159, 160, 161, 168} Also, non-tumorous increase of the basophile cells in the pituitary and mere hyperplasia of the suprarenals have been frequently observed in cases of hypertension.^{23, 77, 78} Both features seem to be causally connected with each other through the "corticotropic" and "adrenotropic" activity of the pituitary anterior lobe. The latter may be increased even in those numerous cases of hypertension where no distinct morphological changes are found in the pituitary.¹⁷⁵

The findings above mentioned apply not only to hypertension but also to arteriosclerosis in general which is intensely promoted through anterior pituitary and suprarenal activity^{23, 79, 80} (table 2) even in infants.¹⁵⁷

CLINICAL FACTS

Central Hypertension. The following features indicate at least a participation of central nervous system pathogenic factors in the origin of "essential" hypertension:

(1) Fall of hypertensive blood pressure during sleep,^{81, 82} during narcosis,⁸³ and during spinal anesthesia.^{84, 85}

(2) Fall of hypertensive blood pressure during loss of CO₂ through hyperventilation,^{11, 86, 87, 88, 89, 90, 91, 92, 93} a phenomenon which is completely or almost completely absent in normals^{93, 94, 95, 96} and in purely "nephritic" hypertension (table 3, figures 3, 4, 5).^{16, 90, 93} It corresponds to the experimental findings in animals whose brain stem has been artificially acidified.¹⁰ Its origin is a central one and it is abolished in hyperventilation with gaseous mixtures containing sufficient CO₂ to maintain the alveolar CO₂ level unchanged (see figure 5).

(3) Fall of hypertensive blood pressure during diathermy of the skull^{12, 97} in about 50 per cent of the cases, probably due to improvement of cerebral blood flow (table 4).

(4) Fall of hypertensive blood pressure after lumbar puncture.⁶⁸

TABLE IV

Response of Blood Pressure Level to Diathermy of the Skull (Raab¹²)

Type of Cases	No. of Cases	No. of Experiments	Average Blood Pressure Level mm. Hg	Average of Maximum Responses of Blood Pressure During Diathermy of the Skull. mm. Hg
Normals	12	12	113	+ 1
Reacting cases of "essential" and nephrosclerotic hypertension (about 50%)	15	47	192	-31

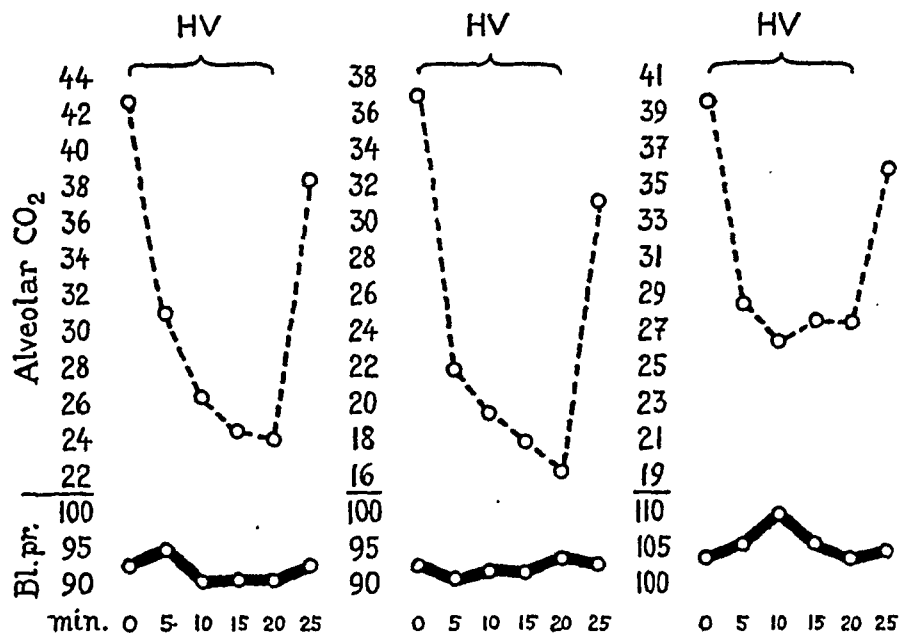


FIG. 3. Response of alveolar CO₂ and systolic blood pressure to hyperventilation (HV) in normals. (Raab.¹¹)

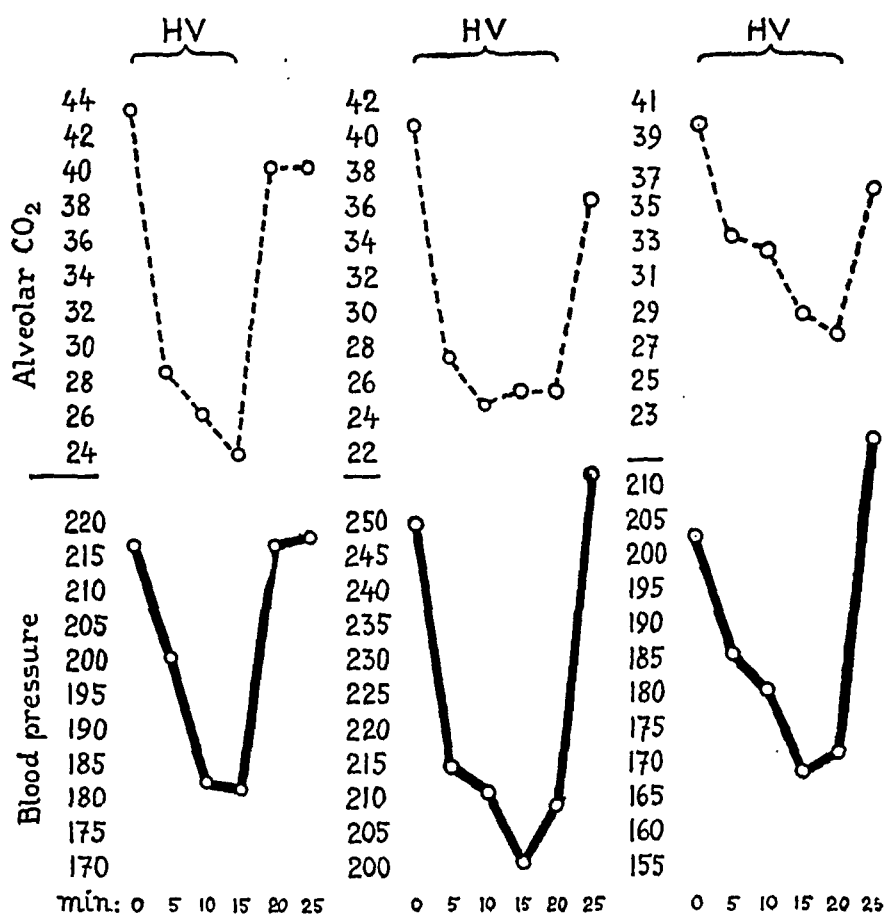


FIG. 4. Response of alveolar CO₂ and systolic blood pressure to hyperventilation in "essential" hypertension, indicating central vasomotor hyperirritability. (Raab.¹¹)

(5) The vasopressor response to inhalation of CO_2 is much greater in both hypertensive and non-hypertensive elderly persons than it is in young normals and in patients with nephritic hypertension.^{19, 98, 99} Its abnormal increase corresponds to experimental findings in animals with anoxemia or direct acidification of the brain.^{10, 24} It may be mentioned here that the

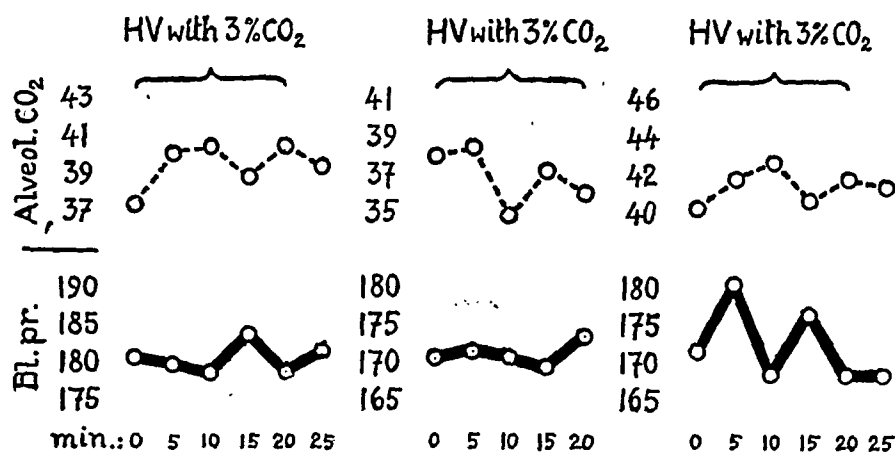


FIG. 5. Response of alveolar CO_2 and systolic blood pressure to hyperventilation with 3 per cent CO_2 in "essential" hypertension, demonstrating that prevention of loss of CO_2 also prevents the fall of blood pressure. This is evidence against the belief of some authors that the fall of blood pressure during hyperventilation is due to mechanical factors such as movements of the diaphragm, etc. (Raab.¹¹)

average response to quantitatively standardized CO_2 stimuli, as determined with a special technic, increases steadily with advancing age (figure 6).¹³ This is probably due to the gradual decrease in blood and oxygen supply^{58, 62, 63, 64, 65, 66} and to a corresponding increase in irritability of the cerebro-medullary vasoconstrictor centers.

(6) Diminished vasopressor response of hypertensive patients to CO_2 inhalation following administration of padutin,¹⁷ which exerts a distinct dilatory effect upon the brain vessels (table 5).^{100, 101}

TABLE V

Response of Blood Pressure Level and of Central Reactivity to CO_2 under the Influence of Various Drugs in "Essential" and Nephrosclerotic Hypertension (Raab and Friedmann¹⁷)

Preparation Used	Dose	Duration of Experiments (Minutes)	No. of Experiments	Average Blood Pressure Level mm. Hg	Average Response	
					of bl. pr. level mm. Hg	to CO_2 -test mm. Hg*
Morphine hydrochloride	0.02 gm. s.c.	60-105	3	165	- 6	-45
Luminal	0.1-0.2 gm. p.o.	60-120	12	162	± 0	-12
Padutin (Kallikrein)	24 units s.c.	20	13	173	+ 4	-18
Carbaminoylcholine-chloride (Doryl)	0.25 mg. s.c.	20-30	9	180	-23	+ 8

* The figures in this column indicate the difference in the degree of the blood pressure elevating effect of a standard CO_2 stimulus between the patients examined in this series and the average response of 25 persons of the same age groups.

(7) Increased vasopressor response to physical work,^{16, 102} to holding the breath,^{103, 104} to psychic emotion,¹⁰² to pain,^{105, 106} to cold,^{107, 108} and to stimulation of the trigeminal nerve through the nose.^{109, 110}

The increased blood pressure response to sensory stimuli corresponds to the reaction of animals with artificial acidification of the vasomotor centers.¹⁰

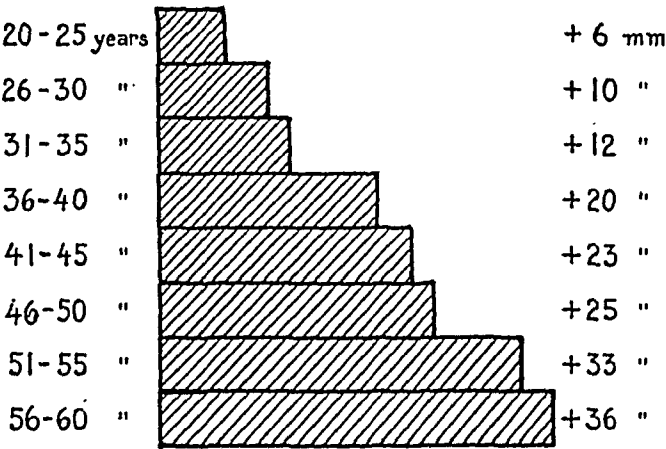


FIG. 6. Central vasomotor irritability increases with advancing age. The diagram shows the elevations of blood pressure due to a standard CO₂ stimulus (inhalation of CO₂ gradually increasing from 0 per cent to 7 per cent within 6 minutes) in 200 individuals with a normal blood pressure level. Every age group consists of 25 cases. (Raab.¹³)

(8) The average oxygen utilization of the circulating brain blood is increased in hypertensive patients,¹⁰² probably due to diminution of the cerebral circulatory volume (table 6).

TABLE VI

Cerebral Oxygen Utilization (Determined through Puncture of an Artery and of the Vena Jugularis Interna at the Base of the Skull) (Raab¹⁴)

Type of Cases	No. of Cases	O ₂ -utilization in the Brain in % of the Arterial O ₂ (average)	Investigators
Normals	10 81	35 34*	Raab Lennox
"Essential" and nephrosclerotic hypertension	10 7	43 43*	Raab Weiss and Ellis

* These figures were calculated from unpublished records which Dr. Wm. Lennox and Dr. Soma Weiss had been kind enough to lend me for comparison in 1930.

Some of the above mentioned phenomena are incompatible with the assumption of a purely renal pathogenesis of essential hypertension. They indicate, on the contrary, a participation of central factors in a large proportion of cases, thus corroborating a number of established experimental and morphological facts.

Renal Hypertension. It is unnecessary to discuss the symptoms which reveal to the clinician the presence of renal arteriolosclerosis. They are sufficiently well known, and as soon as any of them appear the term "essential" hypertension is no longer valid, as it refers to cases with no *clinical* signs of renal involvement.

Hormonal Hypertension. An increased anterior pituitary and supra-renal activity in "essential" hypertension as it is suggested by anatomical findings (see above) may also be deduced indirectly from certain clinical features, such as the common occurrence of hypertension in Cushing's syndrome and at the time of the menopause. An increased anterior lobe secretion is known to prevail in the aforementioned conditions and accordingly abnormally high amounts of prolan, of the corticotropic hormone of the anterior lobe, and of cortin have been found in the blood not only of these particular types of patients¹⁶⁰ but in essential hypertension in general.^{111, 112, 113} The importance of anterior pituitary function for blood pressure regulation becomes evident from a statistical comparison of blood pressure levels in various primary hypophyseal disorders (table 7).

TABLE VII
Blood Pressure in Primary Hypophyseal Disturbances

Type of Hypophyseal Disturbance		No. of Cases	Average Age (Years)	Minimum Systol. Bl. Pr. (mm. Hg)	Maximum Systol. Bl. Pr. (mm. Hg)	Average Systol. Bl. Pr. (mm. Hg)	Normal Average Systol. Bl. Pr. at Corresponding Age (mm. Hg)
Hyperfunction of anterior lobe	Basophile Adenoma	25	29	95	300	189	120
	Acromegaly	24	45	104	270	142	140
Hypofunction of anterior lobe	Simmonds' disease	42	42	50	155	80	136
	Froehlich's disease and hypophyseal dwarfism	13	23	60	125	96	114

These figures were calculated from data collected by A. Ruggieri in Vienna hospitals and from the literature.—The "normal" blood pressure values were calculated from several statistical publications of the literature.

Whether the powerful vasopressor and corticotropic substance "hyper-tonin," which Westphal and Sievert⁸ discovered in the serum ultrafiltrates of hypertensive patients, originates in the hypophysis is not yet decided. Hantschmann's work¹¹⁴ seems to support this view. Other technical methods have failed to demonstrate the regular presence of abnormal amounts of hormonal vasopressor substances in the blood^{115, 116, 117} and in the cerebrospinal fluid¹¹⁸ of patients with permanent essential hypertension.

The manifold contradictions in the extensive literature on blood adrenalin in essential hypertension have been clarified in part by Konschegg.^{42, 43} He comes to the conclusion that the vasoconstrictor effect of the usually normal amounts of adrenalin which are found in the blood of essential hypertensives is intensified through the formation of abnormally vasoactive compounds with cortical lipoids. In recent chemical investigations of the author, which will be published elsewhere,¹⁷⁰ there have been confirmed both the presence of normal adrenalin levels in the blood of essential hypertensives at rest and the formation of compounds of adrenalin with cortical sterols ("AC" compounds). Abnormally intense discharges of these AC compounds into the blood stream after bodily exercise were found in the majority of 25 cases of essential hypertension.¹⁷⁰ Also, during attacks of paroxysmal rise of blood pressure, which do not strictly belong in the group

TABLE VIII

Name	Age	Sex	Number of Series of Irrad.	Degree of Subjective Improvement	Duration of Improvement (Months)	Bl. Pr. Before Irrad. mm. Hg	Bl. Pr. at End of Observation mm. Hg
M. K.	47	♀	1	+++	24	230	270
M. H.	65	♀	2	+++	16½	220	196
D. T.	74	♂	1	+++	14	210	230
F. H.	72	♂	3	+++	12	210	220
J. S.	75	♂	3	+++	8	200	190
F. Z.	60	♂	1	++	3½	210	220
P. S.	53	♂	1	++	6	200	215
A. U.	61	♂	4	+	12	200	166
Average	63		2		12	210	213

Hypertensive patients with angina pectoris whose anginal attacks disappeared completely or partly after roentgen irradiation of the suprarenal glands while the blood pressure level remained practically unchanged. This speaks against a predominant rôle of suprarenal activity in the maintenance of stable essential hypertension (Raab²⁰).

of "essential" hypertension, the adrenalin level of the blood has been found abnormally high.^{117, 119} Roentgen-irradiation of the suprarenal glands is apt to prevent these attacks.²¹ They are due either to a tumor or to a merely functional state of hyperactivity of the suprarenal glands. In ordinary essential hypertension, however, roentgen-irradiation of the adrenal glands, as a rule, does not depress the blood pressure level; not even in those numerous cases in which a reduction of adrenalin discharges during exercise, emotion, cold, etc., is evidenced by complete or almost complete and long-lasting relief of coexisting angina pectoris after roentgen treatment (table 8).²⁰

CLINICAL DIFFERENTIATION OF PATHOGENIC FACTORS

Both cerebromedullary and renal arteriosclerotic ischemia can be present and can cause arterial hypertension despite the complete absence of the common clinical manifestations of cerebral and renal sclerosis.

Central Factors. Central vasomotor hyperirritability can be detected at normal or moderately elevated blood pressure levels through an increased vasopressor effect of measured CO_2 inhalation,^{10, 98, 99} of holding the breath,^{103, 104} etc. These methods are not reliable, however, at high blood pressure levels because the constrictive power of the vessel walls is limited. The hyperventilation test (drop of systolic pressure during 15 minutes of slow, deep respiration) gives somewhat clearer information. It is usually

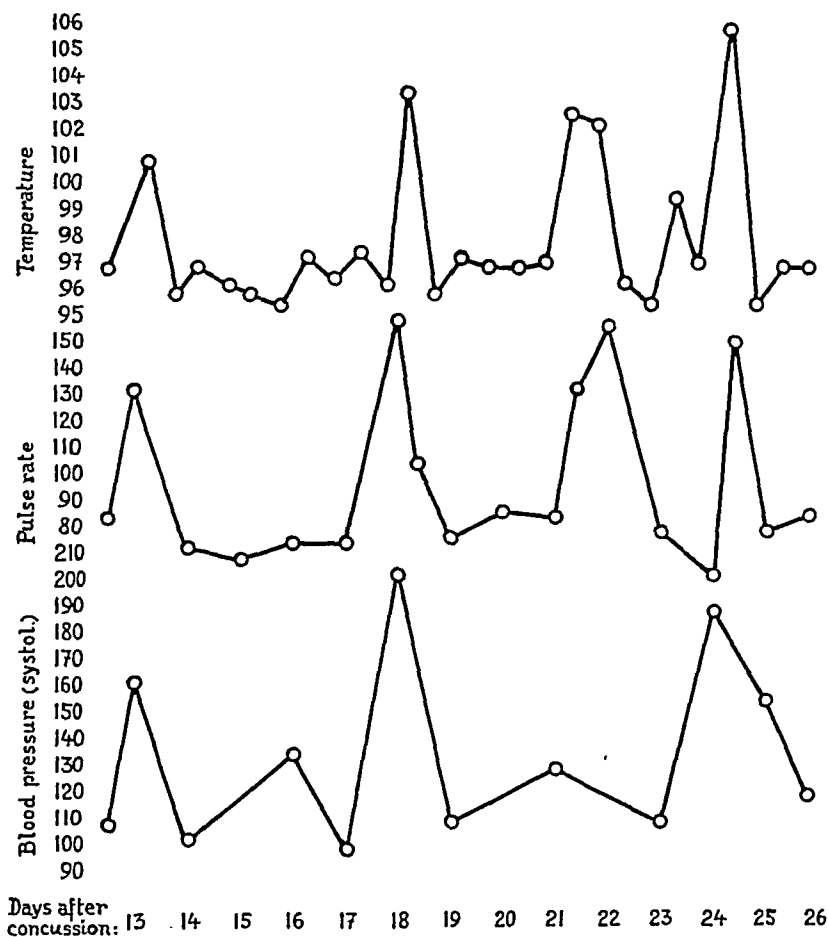


FIG. 7. Attacks of centrogenous arterial hypertension with fever and tachycardia after concussion of the brain in a 45 year old woman. (Raab.²²)

negative in normals,^{93, 94, 95, 96} in purely nephritic hypertension,^{10, 90, 93} and in a minority of cases of "essential" hypertension without clinical kidney symptoms.^{10, 96, 121} It is usually positive in essential hypertension but sometimes also in "chronic nephritis."¹²¹ Its significance consists exclusively in revealing the presence of a central hyperirritative pathogenic factor without indicating or excluding any other factors which may or may not be present at the same time. This is likewise true for other functional tests of central activity previously mentioned.

Arterial hypertension due to infectious, toxic or traumatic lesions of the vasomotor centers can be identified through the case history (poliomyelitis, encephalitis, CO-poisoning, concussion, etc.). The traumatic types of central hypertension appear sometimes in attacks which are associated with tachycardia and fever (figure 7).^{22, 122}

Renal Factors. The appearance of clinical symptoms of arteriosclerosis of the kidneys, such as albuminuria, hyposthenuria, etc., indicates directly the probable presence of a renal pathogenic factor in arterial hypertension. In these cases the hypertension is usually no longer called "essential" although the pathogenesis remains in principle the same. Before the

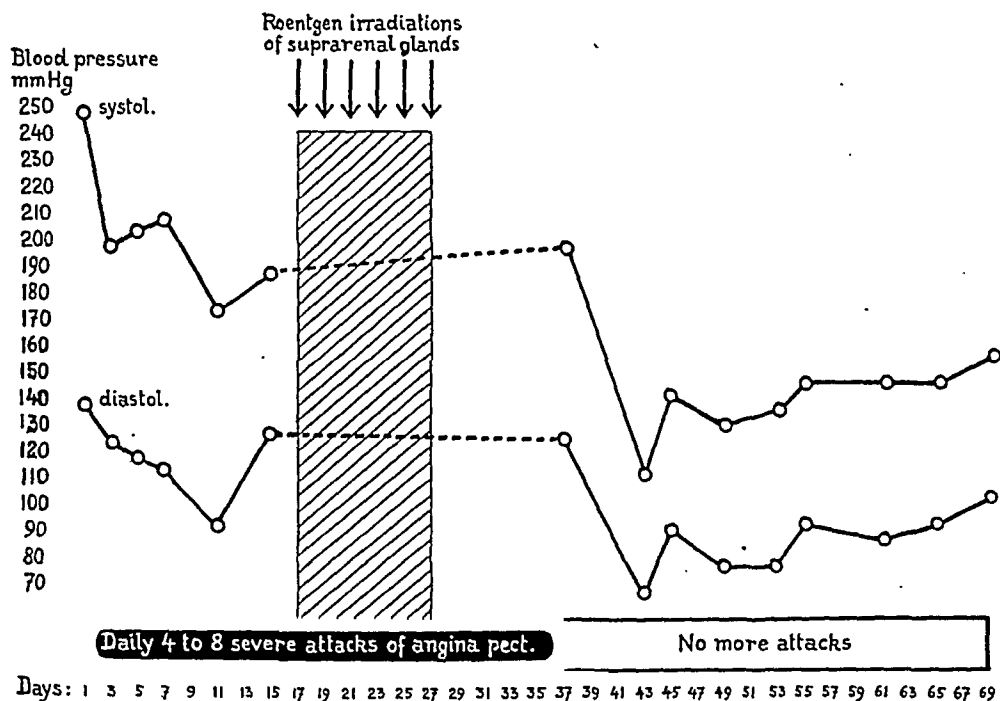


FIG. 8. Hypertension of apparently hormonal type in a woman aged 45 with severe attacks of angina pectoris relieved by roentgen irradiation of the suprarenal glands. The interval of about two weeks between treatment and clinical effect corresponds to the usual time of reaction to irradiation of the suprarenal glands.

onset of clinical kidney symptoms a prevailingly or exclusively renal origin of hypertension may be concluded indirectly from a negative hyperventilation test, high diastolic pressure, pale skin,¹²³ a history of pyelitis,¹⁷² etc.

Hormonal Factors. The hormonal nature of hypertension is obvious in the presence of the typical features of Cushing's syndrome, such as purplish striae, obesity, "moon face," osteoporosis, hirsutism, etc. It is probable, if hypertension develops at the age of the menopause (figure 8) and in early diabetes. Tumors of the adrenal glands and paragangliomas with hormonal discharges may be diagnosed functionally from the acuity and characteristics of the attacks of hypertension (Pal's blood pressure crises¹⁰⁵) and topically

from the pyelogram and the roentgen-ray picture after perirenal oxygen insufflation. A sudden intense rise of blood pressure immediately after massage of the adrenal region either on the right or left side may facilitate the localization of an adrenal tumor. A recently published modification of Shaw's method for the chemical assay of adrenalin in blood, which reveals the circulating amounts of adrenalin-cortical sterol ("AC") compounds,¹⁷¹ yields normal values in plain essential hypertension but abnormally high ones in hypertension with renal insufficiency and in severe cardiac decompensation. In a two year old infant with periods of intense hypertension¹⁷⁰ abnormally high values were also found during the latter (figure 9).

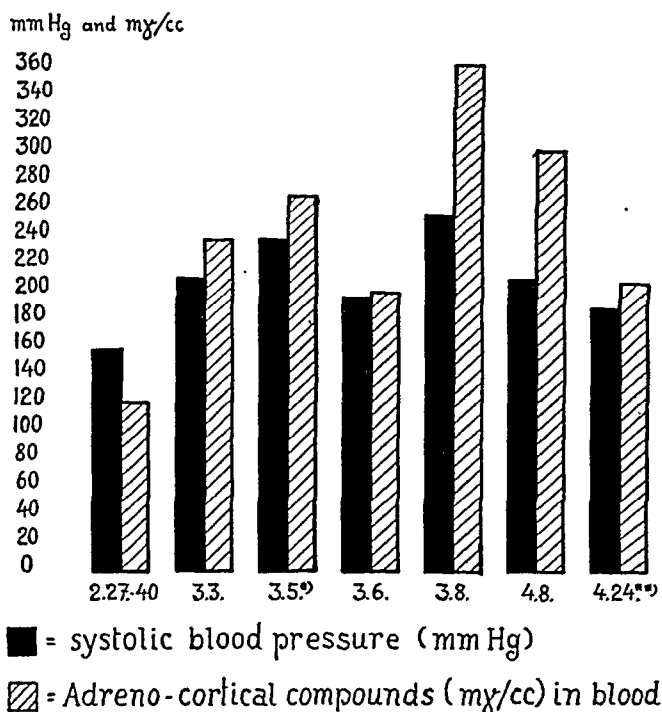


FIG. 9. Hypertension with slight renal involvement in a 2 year old child. In this case there was a closer parallelism of blood pressure and adreno-cortical compound level in the blood than in ordinary essential hypertension.

* After massage of right suprarenal region.

** In narcosis; 30 minutes after exposure of kidneys and suprarenal glands which showed no gross anomalies.

The stabilization of a previously labile blood pressure on a high level indicates the establishment of arteriosclerotic vascular lesions in brain and kidneys, usually on a hormonal basis. The continuously repeated discharges of abnormally large amounts of suprarenal "AC" compounds into the blood stream, which are characteristic for "essentially" hypertensive individuals,¹⁷⁰ and the storage of these compounds in the vascular wall tissue¹⁸² make the suprarenal glands appear to be the most important endocrine organs in this respect.

PROPHYLAXIS AND THERAPY

Prophylactic measures against essential hypertension have to be directed primarily against anterior pituitary and suprarenal hyperactivity and against a constitutional predisposition to such hyperactivity. The following theoretical possibilities may be mentioned:

(1) Avoidance of generation by mates with a definitely arteriosclerotic and hypertensive pedigree;

(2) Lifelong avoidance of excessive amounts of foodstuffs which both stimulate the suprarenal glands and damage the vessel walls directly, namely cholesterol and ergosterol (vitamin D) in egg yolk, butter-fat and other animal fats;

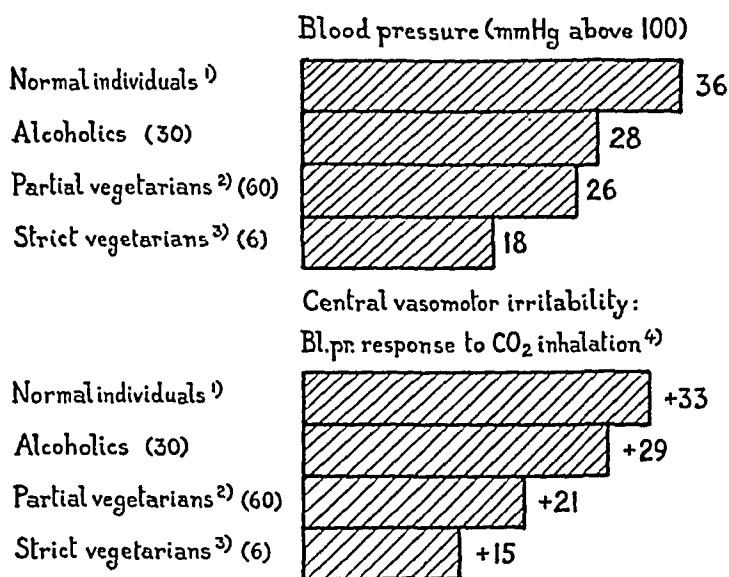


FIG. 10. The average age of each group was from 52 to 53 years.

1. The "normal" blood pressure level for the age of 53 years was calculated from several statistical publications of the literature.

2. Persons having refrained from meat but not from eggs and dairy products for an average period of 19 years.

3. Persons having refrained from all kinds of animal food including eggs and dairy products for an average period of 4 years.

4. The CO₂ standard stimulus was applied by inhalation of CO₂ gradually increasing from 0 per cent to 7 per cent within 6 minutes. An elevation of 33 mm. Hg is the normal average response of the blood pressure to this test at the age of 51 to 55 years. (Raab and Friedmann.¹⁸⁾)

International statistics, the results of a world wide inquiry by the author ¹⁵ and many experimental observations demonstrate the importance of the alimentary intake of large amounts of lipoids as a probable partial factor in the occurrence of arteriosclerosis and hypertension. ^{15, 124}

Some investigations which have been carried out in vegetarians show a lower average blood pressure level and a lesser central vasomotor irritability ^{125, 18} than in normally fed individuals of analogous age (figure 10);

(3) Avoidance of excessive tobacco smoking because of the adrenergic and arteriosclerosis-enhancing effect of nicotine¹²⁶;

(4) Avoidance of excessive mental strain because of its probable stimulating effect upon the suprarenal glands;

(5) Periodical roentgen-ray irradiation of the pituitary gland and the suprarenals in selected individuals who seem to be particularly endangered according to their pedigree or to an unusually early onset of clinical symptoms;

(6) Administration of sex hormones (chiefly female) in selected cases in due time to slow down climacteric anterior lobe and suprarenal hyperactivity.

Probably none of the measures mentioned above would in itself prove to be a definitely reliable means of protection against arteriosclerosis and hypertension but all of them appear theoretically well enough founded to be practically considered. Some of them have been used successfully in the treatment of hypertension, especially in its earliest stages, and in cases of a prevalingly hormonal vasoconstrictor type; for instance a diet free of eggs, milk, butter and milk-fat in juvenile hypertension¹²⁷ and in a number of adult patients^{128, 129}; roentgen-ray irradiation of the pituitary and adrenal glands in some responding cases of essential hypertension¹³⁰ (see also figure 8), in paroxysmal hypertension²¹ and in Cushing's disease^{131, 132}; administration of sex hormones, particularly in climacteric hypertension.^{45, 133}

There does not exist any satisfactory routine therapy for stabilized essential hypertension of the cerebral and renal arteriolosclerotic type. However, the blood pressure can be temporarily lowered through rest, hyperventilation, diathermy of the skull, sedatives, lumbar puncture, etc., not infrequently with prolonged relief of subjective complaints. The objective results of operative procedures, such as denervation of the suprarenals or the kidneys, are rather irregular and not always convincing.^{134, 135, 136, 137, 138} In one case of malignant hypertension in a young man an excessively high level of adreno-cortical ("AC") compounds was found in the blood despite denervation of the adrenal glands.¹⁷⁰

Encouraging attempts to counteract at least the renal factor in hypertension by the therapeutic administration of vasodepressant kidney extracts have recently been published by Page and co-workers.¹⁷⁸

SUMMARY

The establishment of our knowledge concerning the origin of "essential" hypertension has been greatly hampered for a long time through the endeavors of many investigators to demonstrate one or another single pathogenic factor as being solely responsible for the abnormal elevation of blood pressure. This has led to endless argument, contradiction and confusion. Today we know that various hypertensive mechanisms are, or at least may be, simultaneously present in the great majority of cases. Some of these

mechanisms can be demonstrated directly, as for instance central vasomotor hyperirritability; others may be inferred indirectly from animal experiments and from pathological postmortem findings, as for instance the formation of vasopressor substances in arteriosclerotic kidneys. All pathogenic mechanisms of essential hypertension are originally connected with each other on the basis of a primary functional alteration of the endocrine system:

(1) Increased anterior pituitary activity stimulates suprarenal activity. This is the case in anterior lobe adenomata and both during and after the physiological involution of the gonads probably due to the decrease of their inhibiting influence upon the pituitary gland. Besides there exist also states of primary suprarenal hyperfunction (with or without tumors or hyperplasia of cortex and medulla and paragangliomas).

(2) The suprarenal glands not only produce cortical sterols and adrenalin separately but also compounds of both of these substances, which are apparently formed in the lacunae of the adrenal medulla and whose varying

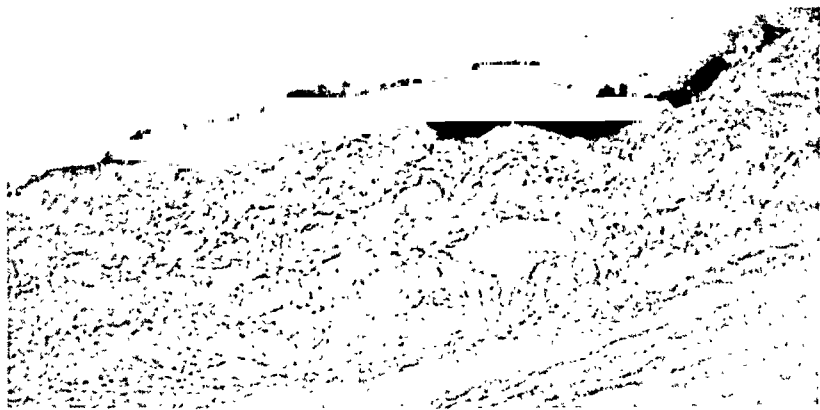


FIG. 11. Atheromatosis (cholesterol deposits) in the intima of rabbit's aorta after 43 days' preparatory treatment with extracts made from 1 liter serum of arteriosclerotic and hypertensive patients and after subsequent cholesterol-feeding (7 gm. in 14 days). In untreated animals it takes at least two months of cholesterol feeding to produce a similar effect. (Raab.²³)

composition seems to be of functional significance. They exert vasoconstrictor effects upon the blood vessels and, furthermore, they damage the arteries in the walls of which they accumulate through (a) degeneration of the media, and (b) marked acceleration of the deposition of alimentary lipoids (cholesterol, phosphatids) in the intima (see figures 1 and 11). In these ways they contribute to the development of arteriosclerosis.

(3) With the progress of arteriosclerotic changes of the small vessels both in the brain-stem, in the medulla oblongata and in the kidneys, two additional comparatively stable vasopressor mechanisms develop: (a) cerebromedullary arteriosclerotic ischemia causing an increased central vasoconstrictor tonus and increased central vasomotor irritability. It contributes to the raising of blood pressure to an abnormally high level and it causes

intensified vasopressor reactions to various stimuli. The objection that, in accepting this theory, one would have to expect simultaneous central dyspnea^{123, 139} is based on a misconception, since the respiratory centers are much less sensitive to shortage of oxygen than the vasomotor centers^{16, 140}; (b) renal arteriolosclerotic ischemia causes elevation of blood pressure through formation of vasopressor substances in the ischemic kidneys (renin which is later activated to angiotonin), possibly with sensitizing participation of a suprarenal hormonal factor.

(4) Every one of the three causally interrelated vasoconstrictor mechanisms, hormonal, central and renal, may appear alone, but usually all of them are present in the same case, although in a varying distribution. They can be clinically identified to a certain extent.

CONCLUSIONS

A survey of the international literature and of some original work leads to the following conclusions:

"Essential" hypertension can be caused by three pathogenic factors:

- (1) Vasoconstriction due to hormonal effects upon peripheral vascular tonus (factor H). This mechanism is usually of only minor importance.
- (2) Vasoconstriction due to increased central vasomotor tonus and irritability (factor C).
- (3) Vasoconstriction due to formation of vasopressor substances in the kidneys (factor R).

The hormonal factor H is probably caused by a primary cortico-adrenotropic hyperactivity of the pituitary anterior lobe and a secondary, or also primary, hyperactivity of the suprarenal glands; the central factor C is caused by arteriolosclerotic ischemia and acidification of the cerebromedullary vasomotor centers; the renal factor R is caused by arteriolosclerotic ischemia of the kidney tissue.

There is a very close causal relationship between these three factors. Arteriosclerotic changes of the arteries are greatly enhanced by vasoactive compounds of cortical lipoids (sterols) and adrenalin. The suprarenal glands thus contribute directly to the factor H and indirectly to the factors C and R.

The pathogenic factors H, C and R can be present or partly absent in varying quantitative distributions. Renal changes are not infrequently completely lacking both macroscopically and microscopically.

For an approximate clinical characterization of the prevailing pathogenic mechanisms in individual cases of hypertension the terms "H type," "HR type," "CR type," etc., are suggested.

Prophylactic and therapeutic possibilities are briefly discussed.

BIBLIOGRAPHY

1. HEYMANS, C.: Some aspects of blood pressure regulation and experimental arterial hypertension, *Surgery*, 1938, iv, 487-501.
2. KOCH, E., MIES, H., and NORDMANN, H.: Arterieller Hochdruck durch Daueraus-schaltung der Blutdruckzügler, *Ztschr. f. Kreislaufforsch.*, 1927, xix, 585.
3. HEYMANS C., BOUCKAERT, J. J., and REGNIERS, P.: *Le sinus carotidiens*, 1933, Doin & Co., Paris.
4. DIXON, W. E., and HELLER, H.: Experimentelle Hypertonie durch Erhöhung des intra-kraniellen Druckes, *Arch. f. exper. Path. u. Pharmakol.*, 1932, clxvi, 265-275.
5. NOWAK, J. G., and WALKER, I. J.: Experimental studies concerning the nature of hyper-tension, *New England Jr. Med.*, 1939, ccxx, 269-274.
6. HARTWICH, A.: Der Blutdruck bei experimenteller Urämie und partieller Nierenaus-scheidung, *Ztschr. f. d. ges. exper. Med.*, 1930, lxix, 462-481.
7. GOLDBLATT, H., LYNCH, J., HANZAL, R. F., and SUMMERVILLE, W. W.: Studies on ex-perimental hypertension. The production of persistent elevation of systolic blood pressure by means of renal ischemia, *Jr. Exper. Med.*, 1934, lix, 347-379.
8. WESTPHAL, K., and SIEVERT, CH.: Ueber den Reizstoff der genuinen Hypertonie, *Ztschr. f. klin. Med.*, 1938, cxxxiii, 223-370.
9. HASSELBACH, H. VON: Bestehen Beziehungen zwischen Veränderungen am Sinus caro-ticus und der Hypertonie?, *Beitr. z. path. Anat. u. z. allg. Path.*, 1931, lxxxvi, 369-374.
10. RAAB, W.: Central vasomotor irritability (contribution to the problem of essential hypertension), *Arch. Int. Med.*, 1931, xlvii, 727-758.
11. RAAB, W.: Die Beziehungen zwischen CO₂-Spannung und Blutdruck bei Normalen und Hypertonikern, *Ztschr. f. d. ges. exper. Med.*, 1929, lxviii, 337-370.
12. RAAB, W.: Diathermie des Hirnstammes bei arteriellem Hochdruck, *Ztschr. f. klin. Med.*, 1931, cxviii, 181-192.
13. RAAB, W.: Funktionsprüfung des zentralen Vasomotorenapparates in verschiedenen Lebensaltern, *Ztschr. f. klin. Med.*, 1931, cxviii, 618-629.
14. RAAB, W.: Hirnblutuntersuchungen bei Hypertonie, *Ztschr. f. klin. Med.*, 1931, cxv, 577-581.
15. RAAB, W.: Alimentäre Faktoren in der Entstehung von Arteriosklerose und Hypertonie, *Med. Klin.*, 1932, No. 14/15.
16. RAAB, W.: Die zentrogenen Formen des arteriellen Hochdruckes, *Ergebn. d. inn. Med. u. Kinderh.*, 1934, xlv, 452-555.
17. RAAB, W., and FRIEDMANN, R.: Zur Pharmakologie der menschlichen Vasomotoren-zentren, *Ztschr. f. klin. Med.*, 1936, cxxix, 468-490.
18. RAAB, W., and FRIEDMANN, R.: Das Verhalten der Kreislaufsorgane bei "Vegetariern" und Alkoholikern, *Ztschr. f. klin. Med.*, 1936, cxxx, 505-534.
19. RAAB, W., and REDLICH, F. K.: Quantitative Erregbarkeitsprüfung der Vasomotor-enzentren bei verschiedenen Hochdruckformen, *Ztschr. f. klin. Med.*, 1936, cxxix, 455-467.
20. RAAB, W.: Angina pectoris simplex und haemodynamische Herzbelastung, *Ztschr. f. klin. Med.*, 1938, cxxxiv, 595-603.
21. RAAB, W., and SCHÖNBRUNNER, E.: Blut-Jod und Angina pectoris, *Ztschr. f. klin. Med.*, 1939, cxxxvi, 354-361.
22. RAAB, W.: Anfälle von Hochdruck, Tachycardie und Fieber nach Gehirnerschütterung, *Ztschr. f. klin. Med.*, 1939, cxxxvi, 362-366.
23. RAAB, W.: Arterioskleroseentstehung und Nebennierenlipoid-Adrenalin-("NLA")-Komplex, *Ztschr. f. d. ges. exper. Med.*, 1939, cv, 657-678.
24. HEYMANS, C., and BOUCKAERT, J. J.: Sur la pathogénie de la hypertension artérielle; Rôle du CO₂ et de l'oxygène, *Compt.-rend. Soc. de biol.*, 1932, cxi, 145.
25. GOLDBLATT, H.: The pathogenesis of experimental hypertension due to renal ischemia, *ANN. INT. MED.*, 1937, xi, 69-103.

26. ENGER, R., LINDER, F., and SARRE, H.: Die Wirkung quantitativ abgestufter Drosselung der Nierendurchblutung auf den Blutdruck, *Ztschr. f. d. ges. exper. Med.*, 1938, civ, 1-9.
27. COLLINS, D. A.: Hypertension from constriction of the arteries of denervated kidneys, *Am. Jr. Physiol.*, 1936, cxvi, 616-621.
28. FREEMAN, N. E., and PAGE, I. H.: Hypertension produced by constriction of the renal artery in sympathectomized dogs, *Am. Heart Jr.*, 1937, xiv, 405-414.
29. ENGER, R., and GERSTNER, H.: Der Einfluss der Niere auf den Blutdruck nach ihrer völligen Lösung aus dem Gewebszusammenhang des Organismus, *Ztschr. f. d. ges. exper. Med.*, 1938, cii, 413-423.
30. PAGE, I. H.: The effect of bilateral adrenalectomy on arterial blood pressure of dogs with experimental hypertension, *Am. Jr. Physiol.*, 1938, cxxii, 352-358.
31. COLLINS, D. A., and WOOD, E. H.: Experimental renal hypertension and adrenalectomy, *Am. Jr. Physiol.*, 1938, cxxiii, 224-232.
32. ENGER, R., LINDER, F., and SARRE, H.: Die Erzeugung eines renalen Hochdruckes bei hypophysen- und nebennierenlosen Hunden, *Ztschr. f. d. ges. exper. Med.*, 1938, civ, 10-14.
33. ROGOFF, J. M., NIXON, E. N., and STEWART, G. W.: The adrenals in experimental hypertension, *Proc. Am. Physiol. Soc.*, 1939, 197.
34. WOLF, H. J., and HEINSEN, H. A.: Tyramin und Nierendurchblutung, *Arch. f. exper. Path. u. Pharmacol.*, 1935, clxxix, 15-23.
35. HARRISON, T. R., BLALOCK, A., and MASON, M. F.: Effects on blood pressure of injection of kidney extracts of dogs with renal hypertension, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 38-40.
36. PRINZMETAL, M., and FRIEDMAN, B.: Pressor effects of kidney extracts from patients and dogs with hypertension, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 122-124.
37. BRAUN, L., and SAMET, B.: Blutdruck und Niere, *Wien. klin. Wchnschr.*, 1933, xlviii, 1471-1472.
38. HELLER, H., and KUSUNOKI, G.: Die zentrale Blutdruckwirkung des neurohypophysären Kreislaufhormons (Vasopressin), *Arch. f. exper. Path. u. Pharmacol.*, 1933, clxxiii, 301-313.
39. BOUCKAERT, J. J.: Au sujet de l'action stimulante vasomotrice centrale des extraits de lobe postérieur d'hypophyse, *Compt.-rend. Soc. de biol.*, 1934, cxvii, 242-245.
40. SELIGSOHN, A.: Ueber die zentrale Blutdruckwirkung der Hypophysenhormone und nicht isotonischer Lösungen, *Wien. Arch. f. inn. Med.*, 1936, xxix, 421-434.
41. PAGE, I. H., and SWEET, J. E.: The effect of hypophysectomy on arterial blood pressure of dogs with experimental hypertension, *Am. Jr. Physiol.*, 1937, cxx, 238-245.
42. KONSCHIEGG, TH.: Adrenalin, Nebennieren und Blutdruck, *Ztschr. f. d. ges. exper. Med.*, 1932, lxxxix, 559-627.
43. VOGT, H.: Untersuchungen über vasopressorische Stoffe bei der essentiellen Hypertonie und beim Kaolinhochdruck des Hundes, *Klin. Wchnschr.*, 1938, p. 1148-1151.
44. CANNON, W. B., and LISSÁK, K.: Evidence for adrenaline in adrenergic neurones, *Am. Jr. Physiol.*, 1939, cxxv, 765-777.
45. STEINACH, E., PECZENIK, O., and KUN, H.: Ueber hormonale Hyperämisierung, insbesondere über den Einfluss der männlichen Sexualhormone und ihrer Kombination mit weiblichem Hormon auf erhöhten Blutdruck und Hypertonus, *Wien. klin. Wchnschr.*, 1938, li, 65, 103, and 134.
46. NORDMANN, H., and MÜLLER, O.: Ueber die Lage eines blutdruckregulierenden Zentrums in der Medulla oblongata, *Verhandl. d. deutsch. Gesellsch. f. Kreilaufforsch.*, 1932, p. 145.
47. SALUS, F.: Zur Frage des bulbären Hochdruckes, *Klin. Wchnschr.*, 1932, p. 1542-1545.
48. BEIGLBOCK, W.: Trauma und Hochdruck, *Ztschr. f. klin. Med.*, 1934, cxxvii, 144-148.
49. WEISSMANN, A.: Ein Fall von traumatisch bedingtem Hochdruck, *Wien. klin. Wchnschr.*, 1935, i, 494-495.

50. HILLER, F.: Ueber cerebrale Kreislaufstörungen nicht-organischer Art, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1933, 182.
51. WEISSBERGER, S.: Quoted by KAUFFMANN, F.¹⁴⁰
52. BORDLEY, J. III, and BAKER, B. M., JR.: A consideration of arteriosclerosis of the cerebral vessels and the pathogenesis of hypertension, Bull. Johns Hopkins Hosp., 1926, xxxix, 229-263.
53. CUTLER, O. J.: Relations of arteriosclerosis of the cerebral vessels to hypertension, Arch. Path., 1928, v, 365.
54. TUTHILL, C. R.: Hypertension in relation to the blood vessels of the medulla oblongata, Arch. Path., 1931, xi, 760-765.
55. RÜHL, A.: Wie weit ist der genuine arterielle Hochdruck anatomisch bedingt?, Deutsch. Arch. f. klin. Med., 1927, clvi, 129.
56. BÜCHNER, F.: Zur Pathogenese der Hochdruckapoplexie, Deutsch. med. Wchnschr., 1936, i, 369-371.
57. HILLER, F.: Ueber flüchtige Hirnsymptome infolge von Kreislaufstörungen, München. med. Wchnschr., 1932, p. 1465-1469 and 1516-1520.
58. NEUBÜRGER, L.: Ueber Hirnveränderungen bei Hypertonikern, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1932, p. 136.
59. BERBERICH, H., and HOTTA, K.: Quoted by WESTPHAL, K., and HERRMANN, F.⁶⁰
60. WESTPHAL, K., and HERRMANN, F.: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes, Ztschr. f. klin. Med., 1925, ci, 566-583.
61. SCHÜRMANN, P., and MACMAHON, H. E.: Die maligne Nephrosklerose; zugleich ein Beitrag zur Frage der Blutgewebsschranke, Virchow's Arch. f. path. Anat., 1933, ccxci, 47-218.
62. HACKEL, W. M.: Ueber den Bau und die Altersveränderungen der Gehirnarterien, Virchow's Arch. f. path. Anat., 1927, cclxvi, 630-639.
63. MÜHLMANN, M.: Zur Frage der Bedeutung der Lipoidsiderose der Hirncapillaren für die Entstehung der Hypertonie und der Arteriosklerose, Virchow's Arch. f. path. Anat., 1927, cclxvi, 712-730.
64. BÖHNE, C.: Die Arten der Schlaganfälle des Gehirnes und ihre Entstehung, Beitr. z. path. Anat. u. z. allg. Path., 1931, lxxvii, 566-612.
65. WOLKOFF, K.: Ueber Atherosklerose der Gehirnarterien, Beitr. z. path. Anat. u. z. allg. Path., 1933, xci, 515-553.
66. KESSLER, L.: Lebensalter und Kapillarfunktion, Ztschr. f. Kreislaufforsch., 1933, xxv, 777.
67. RIEBOLD, G.: Dauernde erhebliche Blutdrucksteigerung als Frühsymptom einer Gehirnarteriosklerose, München. med. Wchnschr., 1917, p. 1390-1392.
68. KAHLER, H.: Die Blutdrucksteigerung, ihre Entstehung und ihr Mechanismus, Ergebn. d. inn. Med. u. Kinderh., 1924, xxv, 265-413.
69. FAHR, TH.: Ueber die Beziehungen von Arteriosklerose, Hypertonie und Herzhypertrophie, Virchow's Arch. f. path. Anat., 1922, ccxxxix, 41-63.
70. MÜLLER, F. VON: Bezeichnung und Begriffsbestimmung auf dem Gebiete der Nierenkrankheiten, Veröffentl. a. d. Gebiete des Mil. San. Wesens, xxi, 65.
71. HERXHEIMER, G., and SCHULZ, K.: Statistisches zum Kapitel Bluthochdruck, Herzhypertrophie, Nierenarteriosklerose, Gehirnblutung nach anatomischen Befunden, Klin. Wchnschr., 1931, p. 433-438.
72. SHAPIRO, S.: Report of a case of essential hypertension of more than 25 years' duration showing no renal arteriolar changes at autopsy, Jr. Lab. and Clin. Med., 1938, xxiv, 60-64.
73. FISHBERG, A. A.: Anatomic findings in essential hypertension, Arch. Int. Med., 1925, xxxv, 650-668.
74. MONAKOW, P. VON: Blutdrucksteigerung und Niere, Deutsch. Arch. f. klin. Med., 1920, cxxxiii, 129-152.

75. BANSI, H. H.: Zur Hypertoniefrage, *Klin. Wchnschr.*, 1925, p. 409-410.
76. KIMMELSTIEL, P.: Benigne Nephrosklerose und arterieller Hochdruck, *Virchow's Arch. f. path. Anat.*, 1933, ccxc, 245-269.
77. KYLIN, E.: *Der Blutdruck des Menschen*, 1937, Steinkopff, Dresden.
78. RUGGERI, A.: Die Bedeutung der Hypophyse für die Pathologie der Blutgefäße, *Ergebn. d. inn. Med. u. Kinderh.*, 1935, xlix, 262-296.
79. DANISCH, F.: Die sympathischen Ganglien in ihrer Bedeutung für die Cholesterinsklerose des Kaninchens, *Beitr. z. path. Anat. u. z. allg. Path.*, 1928, lxxix, 333-399.
80. HUECK, W.: Referat über den Cholesterinstoffwechsel, *Verhandl. d. deutsch. path. Gesellsch.*, Würzburg, 1925, 18-66.
81. ALLBUTT, T. C.: *Diseases of the arteries, including angina pectoris*, 1915, Macmillan & Co., London.
82. BROOKS, H., and CARROLL, J. H.: A clinical study of the effect of sleep and rest on blood pressure, *Arch. Int. Med.*, 1912, x, 97-102.
83. LUNDY, F.: Intravenous anesthesia, anesthesia and analgesia, Sept.-Oct. 1930; *Northwestern Med.*, March, 1924.
84. DEEVER, J. B., and ECKELS, J. C.: The value and limitations of spinal anesthesia, *New England Jr. Med.*, 1930, cciii, 760-771.
85. HYMAN, A. S.: Spinal anesthesia in hypertension, *Jr. Am. Med. Assoc.*, 1933, ci, 1410-1411.
86. TIRALA, L.: Hypertonie und Atmung, *Wien. klin. Wchnschr.*, 1929, p. 137.
87. RAPPAPORT, I.: Blood pressure and respiration. Hyperventilation as a treatment for hypertension, *Jr. Am. Med. Assoc.*, 1929, xcii, 1158-1162.
88. CASTELLANI, E., and GALLONE, L.: L'influenza delle manovre respiratorie sulla ipertensione arteriosa con speciale riguardo all'azione anti-ipertensiva dell'O₂, *Arch. per le sc. med.*, Torino, 1933, lvii, 435-456.
89. CIONINI, F.: *Minerva Medica*, June 2, 1930 (quoted by GREPPI, *Riv. di neurol.*, 1933, ii, 1-25).
90. DICKER, E.: *Acta med. Scandinav.*, 1937, xcii, 461.
91. BOCK, K. A.: Vergleichende Untersuchungen über die Krankheitsgruppe der vaso-neurotischen Diathese, *Ztschr. f. d. ges. exper. Med.*, 1930, lxxii, 561-597.
92. CORBINI, M.: Effetti della iperventilazione polmonare sulla pressione sanguigna, *Riforma med.*, 1932, No. 31.
93. VOIT, K., and CYBA, J.: Das Verhalten des Blutdruckes bei Hyperventilation und Sauerstoffatmung, *München. med. Wchnschr.*, 1933, p. 1466-1468.
94. COLLIER, R. J., DENSHAM, H. B. A. R., and WELLS, H. M.: The influence of respiratory movements on the cutaneous circulation, *Quart. Jr. Exper. Physiol.*, 1927, xviii, 291.
95. SCHNEIDER, E. C.: A study of respiratory and circulatory responses to a voluntary gradual forcing and respiration, *Am. Jr. Physiol.*, 1930, xci, 390-398.
96. PROGER, S. H., and AYMAN, D.: Hyperventilation in arteriolar hypertension, *Jr. Clin. Invest.*, 1933, xii, 335-343.
97. LASZLO, D., and WEISEL, E.: Ueber einige weniger bekannte Anwendungsmöglichkeiten der Diathermie, *Klin. Wchnschr.*, 1930, p. 1576-1578.
98. LUDWIG, W.: Untersuchungen zur Frage der Blutdruckregulation, *Arch. f. exper. Path. u. Pharmacol.*, 1931, clx, 302-316.
99. HARDGROVE, M., ROTH, G., and BROWN, G. E.: The pressor reaction produced by inhalation of carbon dioxide. Studies of patients with normal blood pressure and with hypertension, *ANN. INT. MED.*, 1938, xii, 482-492.
100. FREY, E. K., and KRAUT, H.: Ein neues Kreislaufhormon und seine Wirkung, *Arch. f. exper. Path. u. Pharmacol.*, 1928, cxxxiii, 1-56.
101. REEKE, TH., and WEHRLE, E.: Die Wirkung intravenöser Kallikreingaben auf den Liquordruck, *Ztschr. f. d. ges. exper. Med.*, 1935, xcvi, 398-403.
102. BARÁTH, E.: Arterial hypertension and physical work, *Arch. Int. Med.*, 1928, xlii, 297-300.

103. MOSLER, E.: Der Atemstillstand in tiefer Inspirationsstellung, *Ztschr. f. klin. Med.*, 1913, lxxviii, 133-146.
104. AYMAN, D., and GOLDSHINE, A. D.: The breath holding test. A simple standard stimulus of blood pressure, *Arch. Int. Med.*, 1939, lxiii, 899-906.
105. PAL, J.: Die Gefäßskrisen, 1905, S. Hirzel, Leipzig.
106. CURSCHMANN, H.: Ueber die Wirkung des Schmerzes auf den Blutdruck, *München. med. Wchnschr.*, 1926, p. 1276-1277.
107. HINES, E. A., JR., and BROWN, G. E.: Standard test for measuring variability of blood pressure: its significance as index of prehypertensive state, *ANN. INT. MED.*, 1933, vii, 209-217.
108. AYMAN, D., and GOLDSHINE, A. D.: Cold as a standard stimulus of blood pressure. A study of normal and hypertensive subjects, *New England Jr. Med.*, 1938, ccxix, 650-655.
109. KRAUS, M.: Quoted by CASTEX, M. R.: La hipertension arterial, Buenos Aires, Andreetta, 1929.
110. BING, R.: Blutuntersuchungen an Nervenkranken, *Berlin. klin. Wchnschr.*, 1906, p. 1180-1183.
111. JORES, A.: Die Bedeutung der Hypophyse für die Entstehung des Hochdruckes, insbesondere der essentiellen Hypertonie, *Klin. Wchnschr.*, 1936, i, 841-846.
112. KYLIN, E.: Die Aetiologie der essentiellen Hypertonie, *Klin. Wchnschr.*, 1935, i, 470-473.
113. DICKER, E.: Présence dans les urines des hypertendus essentiels de substances prolaniques, *Compt. rend. Soc. de biol.*, 1937, cxxiv, 303.
114. HANTSCHMANN, L.: Ueber vasokonstriktorisch wirksame Stoffe im Blut mit besonderem Hinblick auf das Problem des Hochdruckes, *Ztschr. f. d. ges. exper. Med.*, 1935, xcvi, 442-467.
115. PAGE, I. H.: Pressor substances from the body fluids of man in health and disease, *Jr. Exper. Med.*, 1935, lxi, 67-96.
116. PICKERING, G. W.: The effect of introducing blood from patients with essential hypertension into other subjects, *Clin. Sci.*, 1936, ii, 185.
117. FRIEDMANN, B., and PRINZMETAL, M.: Vasomotor effects of blood in patients with hypertension and in animals with experimental hypertension, *ANN. INT. MED.*, 1939, xii, 1617-1631.
118. HOYLE, C.: Pituitary secretion in high blood pressure, *Quart. Jr. Med.*, 1933, ii, 549-560.
119. BRANDT, F., and KATZ, G.: Ueber den Nachweis von Adrenalinsekretion beim Menschen. Die akuten Gefäßskrisen, *Ztschr. f. klin. Med.*, 1933, cxxiii, 40-50.
120. YOUNG, F. G.: Permanent experimental diabetes produced by pituitary (anterior lobe) injections, *Lancet*, 1937, ii, 372-374.
121. PICKERING, G. W.: The peripheral resistance in persistent arterial hypertension, *Clin. Sci.*, 1936, ii, 209-235.
122. NAGL, F.: Zur Hochdruckpathogenese, *Wien. klin. Wchnschr.*, 1936, ii, 1114.
123. VOLHARD, F.: Die doppelseitigen hämatogenen Nierenerkrankungen, *Handbuch d. inn. Med. of G. v. Bergmann and Stähelin*, 1931, J. Springer, Berlin, Vol. VI, Sect. 1.
124. LEARY, T.: Atherosclerosis, the important form of arteriosclerosis, a metabolic disease, *Jr. Am. Med. Assoc.*, 1935, cv, 475-481.
125. SAILE, H.: Ueber den Einfluss der vegetarischen Ernährung auf den Blutdruck, *Med. Klin.*, 1930, No. 25.
126. STRAUSS, L. H.: Nikotinwirkungen und -schädigungen, *Ergebn. d. inn. Med. u. Kinderh.*, 1937, lii, 375-438.
127. DOXIADES, E.: Hypertonie und Hypotonie im Kindesalter, *Ztschr. f. Kinderh.*, 1932, liii, 366.
128. ENOCH, D.: Arznei-, Balneo- und Diättherapie der Hypertonien, *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, 1932, p. 105.
129. HARTSILVER, J.: A note on high blood pressure, *Brit. Med. Jr.*, 1935, 449-450.

130. HUTTON, J. H.: Radiotherapeutic treatment of hypertension and diabetes, *Radiology*, 1935, xxiv, 330-340.
131. CUSHING, H.: "Dyspituitarism": twenty years later, *Arch. Int. Med.*, 1933, li, 487-557.
132. JAMIN, F.: Die hypophysäre Plethora, 1935, J. F. Lehmann, München.
133. FELLNER, O. O.: Hormonale Behandlung der Arteriosklerose, *Wien. klin. Wchnschr.*, 1933, p. 828-829.
134. PENDE, N.: *La Medicina Internazionale*, 1935, No. 1.
135. CRILE, G.: *Diseases peculiar to civilized man*, 1934, Macmillan Co., New York.
136. ADSON, W., and BROWN, G. E.: Malignant hypertension, *Jr. Am. Med. Assoc.*, 1934, cii, 1115-1118.
137. PEET, L. S.: *Univ. Hosp. Bull. Univ. of Michigan*, 1935, i, 17.
138. PAGE, I. H., and HEUER, G. J.: The effect of splanchnic nerve resection on patients suffering from hypertension, *Am. Jr. Med. Sci.*, 1937, cxciii, 820-841.
139. PICKERING, G. W.: The problem of high blood pressure in man, *Brit. Med. Jr.*, 1939, i, 1-3.
140. ROBERTS, FF.: The effect of cerebral anemia upon blood pressure and respiration, *Jr. Physiol.*, 1924-1925, lix, 99-120.
141. MCGINTY, D. A.: Lactic acid metabolism of the circulated brain, *Am. Jr. Physiol.*, 1928, lxxxv, 395.
142. COBET, R.: Ueber den Milchsäuregehalt des Gehirnes bei verschiedenen Formen von Atemnot, *Arch. f. exper. Path. u. Pharmacol.*, 1929, cxlv, 140-145.
143. HALDI, J. A., WARD, H. P., and WOO, L.: Differential metabolism in brain tissue as indicated by lactic acid determination, *Am. Jr. Physiol.*, 1927, lxxxiii, 250-253.
144. KRUEGER, R.: *Papers of the Michigan Academy of Science, Arts and Letters*, 1935, xx, 571.
145. KEELE, C. A.: Pathological changes in the carotid sinus and their relation to hypertension, *Quart. Jr. Med.*, 1933, ii, 213-220.
146. SUNDER-PLESSMANN, G.: Untersuchungen über den Bulbus carotidis bei Mensch und Tier im Hinblick auf die "Sinusreflexe" nach H. L. Hering, *Ztschr. f. Anat.*, 1930, xciii, 367.
147. PICKERING, G. W., KISSIN, M., and ROTHSCILD, P.: The relationship of the carotid sinus mechanism to persistent high blood pressure in man, *Clin. Sci.*, 1936, ii, 193-200.
148. SCHNEYER, K.: Klinische Beobachtungen zur Frage des Entzügelungshochdruckes, *Klin. Wchnschr.*, 1937, p. 192-196.
149. KAUFFMANN, F.: *Kreislauf und Nervensystem*, 989, p. 1034 and 1121.
150. DAVISON, CH., and BRILL, N. Q.: Essential hypertension and chronic hypertensive encephalopathy, *ANN. INT. MED.*, 1939, xii, 1766.
151. CREPET, M.: Ueber die Altersveränderungen der Zwischenhirnkapillaren beim Menschen, *Ztschr. f. Altersforschung*, 1939, i, 217-232.
152. FASCILO, J. C.: L'hypertension artérielle par ischémie rénale ne dépend pas des sur-rénales, *Compt.-rend. Soc. de biol., Paris*, 1938, cxxviii, 1130.
153. HEYMANS, C.: Experimental arterial hypertension, *New England Jr. Med.*, 1938, ccxix, 154.
154. HEYMANS, C., NOWAK, J. G., and SAMAAAN, A.: Sur l'action vasomotrice réflexe centrale et périphérique de l'acide carbonique, de l'anoxémie et de l'asphyxie, *Compt.-rend. Soc. de biol., Paris*, 1934, cxvii, 248.
155. BOUCKAERT, J. J., and HEYMANS, C.: Influence of central blood pressure and blood supply on respiratory and vasomotor centers, *Jr. Physiol.*, 1933, lxxix, 49.
156. FAHR, TH.: Maligne Hypertonie, *Klin. Wchnschr.*, 1939, p. 1541.
157. WIESEL, J.: Quoted by Oppenheimer and Fishberg, *Arch. Int. Med.*, 1924, xxxiv, 631.
158. NUZUM, F. R., and DALTON, J. W.: Paroxysmal and persistent hypertension in association with lesions of the adrenal glands, *Am. Heart Jr.*, 1938, xvi, 643-662.
159. BRUNSWIG, A., HUMPHREYS, E., and ROOME, N.: The relief of paroxysmal hypertension by excision of pheochromocytoma, *Surgery*, 1938, iv, 361-370.

160. HEGGLIN, R., and NABHOLZ, H.: Das Nebennierenmarksyndrom, *Ztschr. f. klin. Med.*, 1938, cxxxiv, 161-195.
161. PALMER, R. S., and CASTLEMAN, B.: Paraganglioma of the adrenal gland simulating malignant hypertension, *New England Jr. Med.*, 1938, ccxix, 793-796.
162. FRIEDMAN, B., SOMKIN, E., and OPPENHEIMER, E. T.: The relationship between the suprarenal glands and renin, *Am. Jr. Physiol.*, 1940, cxxviii, 481.
163. GOORMAGHTIGH, N., and GRIMSON, K. G.: Vascular changes in renal ischemia, *Proc. Soc. Exper. Biol. and Med.*, 1939, xlii, 227; xliii, 688.
164. DUNIHUE, F. W., and CANDON, B. H.: Histological changes in the renal arterioles of hypertensive rabbits, *Arch. Path.*, 1940, xxix, 777-784.
165. GROLLMAN, A., HARRISON, T. R., and WILLIAMS, J. R.: The effect of various sterol derivatives on the blood pressure of the rat, *Jr. Pharm. and Exper. Therap.*, 1940, lxix, 149-155.
166. GELHORN, E., and LAMBERT, E. H.: The vasomotor system in anoxia and asphyxia, 1939, The University of Illinois Press, Urbana, Ill.
167. DOCK, W.: Vasoconstriction in renal hypertension abolished by pithing, *Am. Jr. Physiol.*, 1940, cxxx, 1-8.
168. PINCOFFS, M. C.: Paroxysmal hypertension associated with suprarenal tumor, *Jr. Am. Med. Assoc.*, 1929, xciii, 63.
169. ANDERSON, E., and HAYMAKER, W.: Adrenal cortical hormone (cortin) in blood and urine of patients with Cushing's disease, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 610-613.
170. RAAB, W.: Adreno-cortical ("AC") compounds in the blood in "essential" and "renal" hypertension and in congestive heart failure, *Arch. Int. Med.* (in print).
171. RAAB, W.: The presence and chemical determination of adreno-cortical ("AC") compounds in the blood, *Endocrinology*, 1941, xxviii, 325-336.
172. WEISS, S., and BARKER, F.: Pyelonephritis. Its relations to vascular lesions and to arterial hypertension, *Medicine*, 1939, xviii, 221-315.
173. PICK, E. P.: Ueber humorale Uebertragung hohen und niedrigen Blutdrucks, *Wien. klin. Wchnschr.*, 1935, No. 20
174. NEDZEL, A. J.: Histologic changes following vascular spasm in central nervous system (Pitressin episodes), *Arch. Path.*, 1939, xxviii, 697-711.
175. RASMUSSEN, A. T.: The relation of the basophile cells of the human hypophysis to blood pressure, *Endocrinology*, 1936, xx, 673-678.
176. LANGE, F.: Blutdrucksenkung durch körpereigene Substanz, *München. med. Wchnschr.*, 1930, lxxvii, 2095-2097.
177. GROLLMAN, A., WILLIAMS, J. R., and HARRISON, T. R.: The preparation of renal extracts capable of reducing the blood pressure of animals with experimental renal hypertension, *Jr. Biol. Chem.*, 1940, cxxxiv, 115-121.
178. PAGE, I. H., HELMER, O. M., KOHLSTAEDT, K. G., FOUTS, P. I., and KEMPF, G. F.: Reduction of arterial blood pressure of hypertensive patients and animals with extracts of kidneys, *Jr. Exper. Med.*, 1941, lxxiii, 7-41.
179. MUÑOZ, J. M., BRAUN-MENENDEZ, E., FASCILOLO, J. C., and LOLOIR, L. F.: The mechanism of renal hypertension, *Am. Jr. Med. Sci.*, 1940, cc, 608-617.
180. ROBBARD, S., and KATZ, L. N.: The rôle of renal metabolism in hypertension and uremia, *Jr. Exper. Med.*, 1941, lxxiii, 357-364.
181. SANDERS, E.: Ueber die Wirkung von reinem Adrenalin und Nebennierenextrakten per os und am isolierten Organ, *Arch. exper. Path. u. Pharmacol.*, 1938, clxxxviii, 657-668.
182. RAAB, W.: The concentration of adreno-cortical ("AC") compounds in human organ tissues. (Paper in preparation.)
183. McCULLAGH, E. P., and RYAN, E. J.: Use of desoxycorticosterone acetate in Addison's disease, *Jr. Am. Med. Assoc.*, 1940, cxiv, 687-688.

184. GRIFFITH, J. Q., and ROBERTS, E.: Further studies in the mechanism of vascular hypertension following the intracisternal injection of kaolin in rats, *Am. Jr. Physiol.*, 1938, cxxiv, 86-93.
185. JEFFERS, W. A., LINDAUER, M. A., and LUKENS, F. D. W.: Adrenalectomy in experimental hypertension from kaolin, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvii, 260-262.
186. GLENN, F., and LASHER, E. P.: The effect of destruction of the spinal cord on the artificial production of hypertension in dogs, *Am. Jr. Physiol.*, 1938, cxxiv, 106-109.
187. RAAB, W.: The effect of desoxycorticosterone acetate upon the cardiovascular system of normal individuals. (Paper in preparation.)
188. SCHROEDER, H. A., and ADAMS, M. H.: The effect of tyrosinase on experimental hypertension, *Jr. Exper. Med.*, 1941, lxxiii, 531-550.

THE CLINICAL SIGNIFICANCE OF THE LOW OR "FLAT" ORAL GLUCOSE TOLERANCE CURVE*

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DURING the course of a study of sprue and allied deficiency states,¹ low or "flat" oral glucose tolerance curves were observed very frequently in the affected individuals. This was not a novel observation, for other observers had had the same experience, and furthermore, had suggested that this finding serve as a diagnostic aid in the recognition of sprue.^{2, 3}

A review of the pertinent literature revealed considerable difference of opinion on the interpretation of the low oral glucose tolerance curve.^{2, 4, 5, 6} It was felt that before relying too greatly upon the contour of the curve as a diagnostic aid in sprue, a satisfactory explanation of its cause was necessary.

With this point in mind, a series of 90 patients exhibiting "flat" or low oral glucose tolerance curves was studied. These patients constituted all of those with such curves seen in the Vanderbilt Clinic of the Presbyterian Hospital during the period of January 1933 to April 1939 inclusive. It was felt that a careful survey of this group might throw considerable light on the clinical significance of this type of blood sugar response as well as on the reason for its presence in sprue.

METHODS

In accord with the suggestion of Thaysen,² all curves showing less than 40 mg. per cent rise in blood sugar during the two to three hours following the oral administration of glucose were considered low. The dose of glucose was usually 100 gm. by mouth. In a few cases, the dose was 1 gm. per kilogram of body weight. The tests were done in the morning following an overnight fast. Specimens of venous blood and urine were obtained fasting and 30, 60, 120 and 180 minutes after glucose ingestion. The blood analyses were done according to the method of Folin.⁷

RESULTS

A total of 90 patients was observed. Their clinical diagnoses were as listed in table 1.

It is evident that the largest group of patients (28 cases or 31.1 per cent) with low oral glucose tolerance curves was that with dietary obesity. However, too great stress should not be placed on this high percentage, for,

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in this clinic, glucose tolerance tests have been done more often on patients with obesity than on those with any other disorder. It is not the purpose of this paper to report the number of obese subjects exhibiting this phenomenon. However, it can be stated that it is a frequent finding. The significance of this type of curve in obesity is under investigation⁸ and will be made the subject of another report. Suffice it to say that there is little evidence to support the belief that it indicates lack of pituitary secretion in these cases. The explanation lies in the fact that these individuals are often huge consumers of carbohydrate—one confessing to eating, in addition to a liberal diet, one pound of sugar a day for three years! The ingestion of a high carbohydrate diet by normal individuals has been shown by Sweeney⁹ and Himsworth¹⁰ to result in flattened oral glucose tolerance curves or "in-

TABLE I
Clinical States Associated with "Flat" Oral Glucose Tolerance Curves

Diagnosis	Number of Cases	Per cent of Total
Obesity—dietary.....	28	31.1
Renal glycosuria.....	11	12.2
Hypopituitarism.....	3	3.3
Hypothyroidism.....	9	10.0
Malnutrition and anorexia nervosa.....	10	11.1
Vitamin B complex deficiency.....	4	4.4
Hyperinsulinism.....	1	1.1
(??) Hypoglycemia.....	6	6.6
"Normal".....	7	7.7
Hirsutism.....	4	4.4
Epilepsy.....	2	2.2
Migraine.....	2	2.2
Xanthomata.....	2	2.2
Pentosuria.....	1	1.1

creased tolerance" for carbohydrate. Himsworth¹⁰ has studied this problem with much care and has advanced evidence for the belief that the flattening in the oral glucose tolerance curve caused by a high carbohydrate diet is produced by some factor which renders these patients highly sensitive to the effects of insulin. Regardless of the mechanism of its production, it remains established that a high carbohydrate diet alone in a normal individual may cause a flat or low oral glucose tolerance curve. In support of this thesis is the fact that when four of the obese subjects in the present study were placed on reducing diets, within a relatively short time their oral glucose tolerance curves returned toward normal.

The next group consists of 11 cases of renal glycosuria. We do not have quantitative studies of the urinary sugar output in these cases and therefore cannot say with certainty that renal elimination was the sole factor concerned in the production of these curves. It may be that accelerated glycogenesis occurs as a compensation for the renal loss of carbohydrate and contributes to the low curve. These findings emphasize the importance of analysis of urine secreted during the glucose tolerance test.

Group III consists of three patients with hypopituitarism. In these cases, the "flat" curve has been attributed to loss of pituitary secretion which ordinarily serves as an antagonist of insulin. Whether the mechanism is as simple as this is to be doubted in the light of recent experimental work¹¹ which indicates that in hypophysectomized dogs there is decreased absorption of glucose from the intestinal tract.

Group IV consists of nine patients with hypothyroidism. Here too the flatness of the curve has been ascribed to the lack of thyroid antagonism to insulin. However, recent experiments¹² have shown that in rats, thyroidectomy is followed by decreased absorption of glucose from the intestine.

Group V consists of patients with malnutrition. Patients similar to these have been said to have "chronic hypoglycemia."¹³ This would appear to be a misnomer, for at no time do they have blood sugar below the normal range. They are underweight, have anorexia and often psychiatric difficulties. Whether their inability to respond to glucose ingestion with a rise in blood sugar constitutes relative hypoglycemia is a debatable point that will be discussed later. Those with more severe grades of this disorder have been labelled instances of anorexia nervosa. The cause for the low curve in these cases may be found in their dietaries, for these are often poor in fat and consist largely of carbohydrate. In addition to this, vitamin deficiencies are more frequent in these people than has been generally recognized. A deficiency in the vitamin B complex might well account for many of the symptoms and also contribute to the low curve.

Group VI consists of four cases which will be reported in more detail at a later date.¹ These patients present a clinical picture which is thought to represent deficiency of the vitamin B complex. Groen¹⁴ has shown by direct measurements that intestinal absorption of glucose is definitely retarded in patients with deficiencies of the vitamin B complex. This is therefore a factor in the causation of the low oral glucose tolerance curve in this group.

One patient was found to have classical hyperinsulinism and was cured by the removal of an islet cell adenoma. In this connection it is of interest to note that a considerable number of patients (6 cases or 6.6 per cent) with low curves presented clinical symptoms suggestive of hyperinsulinism. Glucose tolerance tests were ordered in many instances with this diagnosis in mind. The presenting complaints of these patients were weakness, sweating, palpitation and nervousness, often relieved somewhat by food. Careful study did not support the view that they were suffering with pancreatic islet cell tumors. However, their inability to respond to glucose ingestion with a rise in blood sugar may account for some of their symptoms. On the other hand, most of the patients exhibiting this type of curve had no marked symptoms of hypoglycemia. Since the method used for determining blood sugar⁷ measures other reducing substances in addition to glucose, it is possible that the patients with symptoms of hypoglycemia had more than the

usual amounts of non-glucose reducing substances in the blood. They would then have low true glucose values, possibly within the hypoglycemic range. Another possibility is that these patients, for some reason develop symptoms of hypoglycemia at higher levels than normal individuals. Obviously, this is a matter which merits further study.

The possible relationship between the low curve and hirsutism (4 cases), migraine (2 cases), epilepsy (2 cases) and xanthomata (2 cases) is not evident at present and the number of cases is too small to merit further comment.

A definite number of "normal" subjects (7 cases or 7.7 per cent) exhibit the low curve. However, in the absence of more complete dietary histories and other clinical details, too much stress cannot be laid upon the occurrence of this group. It is possible that some cause would be found on careful study.

In addition to the conditions enumerated above, a review of the literature indicates that low oral glucose tolerance curves are observed in sprue,^{2, 3, 4} celiac disease,^{2, 6} Addison's disease¹⁶ and scleroderma.¹⁵

From these data, it appears that the low or "flat" oral glucose tolerance curve may be due to a number of known causes. These causes may, furthermore, be classified for the sake of clarity into three main groups:

- A. Poor or slow absorption of glucose from the digestive tract*
- B. Rapid removal of glucose from the blood stream*
- C. Combinations of "A" and "B"*

In table 2, the various clinical states associated with low oral glucose tolerance curves have been classified according to the above grouping. It is to be stressed that this classification is in many instances inadequate but it does have the attribute of simplicity and is presented merely as an aid in studying these cases. For obvious reasons no attempt has been made in this report to discuss the more fundamental mechanisms concerned in the disposal of ingested glucose. For instance, the rôles played by phosphorylation and diffusion in the absorption of glucose have not been defined, mainly because of the controversial nature of this subject at present writing.⁵ As indicated in previous paragraphs, in the light of recent studies, there is room for dispute over the inclusion of certain endocrine disorders under the classification "B."

Sprue, the disorder which stimulated interest in the subject of this report, has been classified under "C" in table 2. To amplify this, it appears that in sprue, the low or "flat" oral glucose tolerance curve is caused by the following factors:

(1) The rate of absorption of glucose from the small intestine is definitely retarded. This has been established by the direct studies of Groen.¹⁴ However, so far as the ultimate absorption of glucose is concerned, the hypomotility of the small intestine which also occurs in sprue may counter-

balance the slower rate and finally result in fairly complete absorption of glucose from the intestinal tract.

(2) The rate of removal of glucose from the blood stream in these cases is at least as rapid as normal and possibly slightly more rapid. This has been established by means of intravenous glucose tolerance curves.^{1, 2}

(3) The diet of patients with sprue is often high in carbohydrate. Furthermore, because of the poor assimilation of fat, the diet that is actually absorbed is largely carbohydrate and protein. As has been indicated above, a high carbohydrate diet in a normal individual may cause a low oral glucose tolerance curve. This undoubtedly contributes to the "flat" curve seen in sprue.

TABLE II

Causes for the Low or "Flat" Oral Glucose Tolerance Curve

A. Poor or Slow Absorption of Glucose from the Digestive Tract

1. Edema, atrophy of mucosa and circulatory disturbances of the stomach and small intestine, e.g. sprue, vitamin B def., celiac disease
2. Inflammatory changes in the small intestine; tuberculosis, (?) ileitis
3. Neoplastic disease; tumors of the small intestine

B. Rapid Removal of Glucose from the Blood Stream

1. Mainly by accelerated glyco-genesis and possibly in part by accelerated glucose combustion by means of
 - (a) Excess of insulin or increased sensitivity to insulin—Hyperinsulinism. High carbohydrate diet
 - (b) Lack of insulin antagonists
 - (1) Lack of adrenal secretion—Addison's disease
 - (2) Lack of pituitary secretion—Simmonds' disease. Hypopituitarism due to tumor or developmental defect. Hypophysectomy
 - (3) Lack of thyroid secretion—Myxedema. Cretinism. Scleroderma (?)
2. Renal excretion Renal glycosuria (phlorizin diabetes ?)

C. Combinations of "A" and "B"

- Sprue
- Malnutrition
- Vitamin B complex deficiency states

When liver extract or other potent therapy is used in sprue, the glucose tolerance curve may become normal.¹ This is probably accomplished by restoration of the small intestine to normal so that all constituents of the diet are well absorbed. Failure to influence the glucose tolerance curve with liver extract may well be due to inability to restore normal function to the small intestine.

However, it must be stressed that if the diet of the sprue patient continues to be high in carbohydrate, the oral glucose tolerance curve may remain "flat" despite the restoration of the small intestine to normal.¹

It is evident from the data presented above that many factors must be considered in interpreting the finding of a low or "flat" oral glucose tolerance curve. Most significant of all is the fact that a diet high in carbohydrate may by itself produce this type of curve. Therefore, before at-

taching diagnostic import to this response in any particular disease, the previous dietary regime of the patient exhibiting this phenomenon must be known. If this fact is kept in mind, many of the diverse and apparently unrelated clinical disorders exhibiting "flat" or low oral glucose tolerance curves may be seen to have one common denominator, the high carbohydrate diet. This does not imply that the type of diet alone is responsible for the contour of the oral glucose tolerance curve, for other forces are also concerned. However, in the present series of cases, in the absence of a disorder of the endocrine glands, the ingestion of a diet high in carbohydrate seems the most important cause for the "flat" oral glucose tolerance curve.

SUMMARY

1. From a study of 90 patients exhibiting low or "flat" oral glucose tolerance curves, the causes for this type of curve have been defined.
2. A previous dietary regime high in carbohydrate is of great importance in causing the low or "flat" oral glucose tolerance curve.
3. This type of curve is not by itself diagnostic of any one disease, but may serve as a useful diagnostic aid.
4. The factors responsible for the low or "flat" oral glucose tolerance curve in sprue are discussed.

BIBLIOGRAPHY

1. LEPORE, M. J.: To be published.
2. THAYSEN, T. E. HESS: Nontropical sprue, 1932, Oxford Univ. Press, London.
3. HANES, F. M., and MCBRYDE, ANGUS: Identity of sprue, nontropical sprue and celiac disease, *Arch. Int. Med.*, 1936, lviii, 1-16.
4. MARTIN, E., and SCICLONOFF, F.: L'interet clinique des courbes basses d'hyperglycemie provoquee, *Presse med.*, 1939, xlvii, 503-506.
5. VERZAR, F.: Absorption from the intestine, 1936, Longmans, Green and Co., London, New York.
6. CRAWFORD, THEODORE: Causation of low blood-sugar curve in coeliac disease, *Quart. Jr. Med.*, 1939, viii, 251-260.
7. FOLIN, OTTO, and WU, H.: System of blood analysis; simplified and improved method for determination of sugar, *Jr. Biol. Chem.*, 1920, xli, 367-374.
8. WERNER, S.: To be published.
9. SWEENEY, J. S.: Dietary factors that influence the dextrose tolerance test; preliminary study, *Arch. Int. Med.*, 1927, xl, 818-830.
10. HIMSWORTH, H. P.: Dietetic factor determining glucose tolerance and sensitivity to insulin of healthy men, *Clin. Sci.*, 1935, ii, 67-94.
11. SOSKIN, S., LEVINE, R., and HELLER, R. E.: Carbohydrate utilization in hypophysectomized dog, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 6-8.
12. ALTHAUSEN, T. L., and STOCKHOLM, M.: Influence of thyroid gland on absorption in digestive tract, *Am. Jr. Physiol.*, 1938, cxxiii, 577-588.
13. DORST, STANLEY E.: Chronic hypoglycemia; problem in carbohydrate metabolism, *Am. Jr. Med. Sci.*, 1938, cxcvi, 688-698.
14. GROEN, JUDA: Absorption of glucose from small intestine in deficiency disease, *New England Jr. Med.*, 1938, ccxviii, 247-253.
15. LONGCOPE, W. T.: Hypoglycemia in scleroderma; metabolism in eight cases with reference to function of glands of internal secretion, *Jr. Am. Med. Assoc.*, 1928, xc, 1-7.
16. ROSENOW, G., and JAGUTTIS: Blood sugar in Addison's disease, *Klin. Wchnschr.*, 1922, i, 358-360.

THE CLINICAL SIGNIFICANCE OF THE BLOOD VOLUME *

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THE total quantity of circulating blood in normal humans and the nature and magnitude of the changes incident to disease have long been of interest to practitioners, but in the main these questions have remained a puzzle. Interest has waxed as new methods have been introduced and waned as they were found wanting. A review of methods extant is not intended. The dye injection method devised by Keith, Rowntree and Geraghty¹ in 1915 has been the most widely used of any, yet the numerous modifications of the original technic that have appeared^{2, 3, 4, 5, 6, 7, 8, 9, 10, 11} indicate a feeling of doubt as to the reliability of the original method.

The results reported in this communication were obtained by the dye method developed by Gregersen, Gibson and Stead¹² as modified for clinical use by Gibson and Evans.^{13a} This method accurately measures the plasma volume, total blood volume being calculated from plasma volume and hematocrit. It has proved to be reliable in this and many other clinics. A comparison of our findings with those obtained by earlier technics would contribute nothing to the purpose of this communication, which is to present certain facts about the blood volume in health and disease to the practitioner in the hope they may be helpful as a therapeutic background.

The Normal Blood Volume. The amount of circulating blood in the human body at rest varies with sex, body size and habitus.^{13b} Males have a much larger total blood volume than females. In thin individuals absolute volume is lower and unit volume (in terms of height, weight or surface area) is higher than in well developed subjects of equivalent physical measurements, and the reverse situation obtains in obese individuals. In a group of 100 normal men and women of from 16 to 76 years of age the average range of total blood volume in relation to height and surface area was as shown in figure 1, the individual deviations from the curves shown being ± 15 per cent. Within these limits normal total blood volume for an individual may be predicted on the basis of physical measurements (figure 1). Assuming the normal hematocrit to be 44 for males and 40 for females, normal plasma and circulating red cell volume may be calculated from the total blood volume.

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In the studies reported herein, height has been used for the prediction of normal volume. In groups of patients with the same disease the average of the individual deviations from predicted normal volume is considered to be the change in blood volume characteristic of that disease.

Chronic Congestive Heart Failure. In chronic congestive heart failure total blood volume always is above normal,^{13c} and the degree of elevation of volume is related to the severity of failure. Thus, average total blood volume in a group of patients with organic heart disease but with neither symptoms nor physical signs of failure was normal; in a group with symptoms but without physical signs of failure slightly above normal; in a group with mild congestive failure about 20 per cent above, and in a group with severe failure 55 per cent above normal. As failure progresses, the hematocrit tends to rise but is rarely over 50.

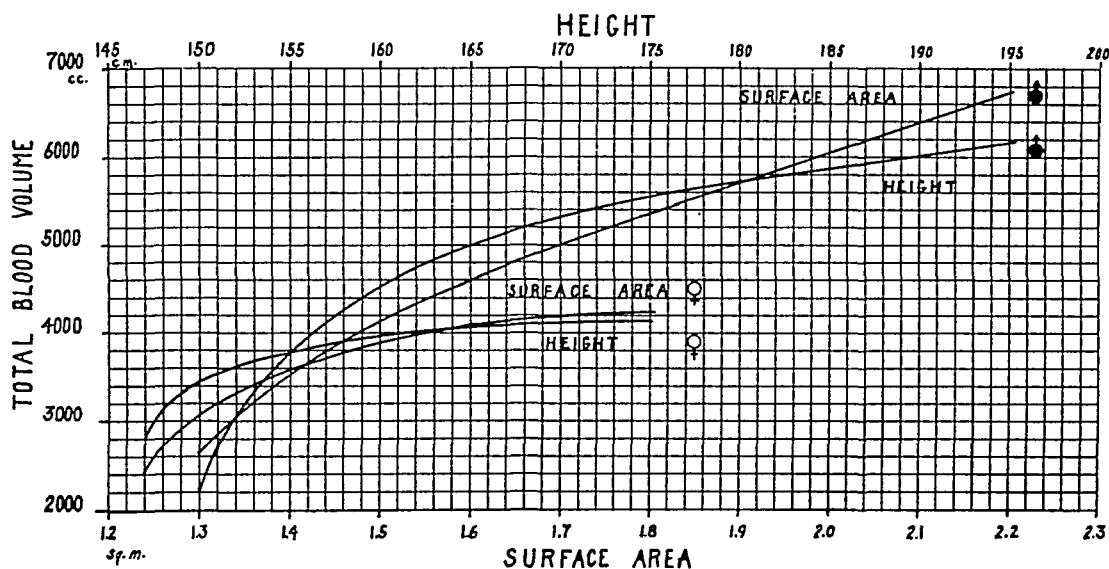


FIG. 1. Nomogram for predicting normal total blood volume in adult men and women. Plasma and circulating red cell volume may be calculated assuming the normal hematocrit to be 44 for males and 40 for females.

The course of the blood volume closely parallels the clinical conduct. Compensation invariably is accompanied by a decrease in total blood volume which may amount to from 500 c.c. to 1500 c.c. There is first a greater reduction in plasma than in circulating red cells so that the hematocrit may rise as the total volume falls. Later, with continued improvement, plasma volume decreases further but at a diminished rate, and the reduction in red cells becomes more rapid so that the hematocrit returns to within normal limits. Once failure has occurred, total blood volume never returns to normal for the individual. The reduction in plasma usually is greatest during periods of most active diuresis.

In cases in which compensation does not occur and in which the patient remains "fixed in failure," or eventually succumbs, blood volume remains

high or increases further. If an intercurrent infection occurs during the course of compensation with a resulting relapse, the blood volume, which had come down from the high level found during the height of failure, will increase again. Recurrent failure is accompanied also by an increase over recovery levels.

The etiology of failure bears little relation to the course of blood volume. Taken as a group, patients with luetic aortic insufficiency do not exhibit as great an increase in volume during failure as do cases with rheumatic valvular disease, "chronic myocarditis," emphysema or hypertension, but the general trends of the volume in failure, compensation or relapse described above are found in all of these classifications.

It is generally recognized that the degree of elevation in venous pressure and slowing in circulation time are fair evidences of the severity of failure. In the four groups of cases with organic heart disease, referred to above, venous pressure and circulation time remained normal until failure occurred, and thereafter, as blood volume increased, there was a parallel and progressive increase in venous pressure and slowing in circulation time. During compensation venous pressure returned to within normal limits before the full reduction in blood volume occurred, but circulation time rarely returned to normal. Thus, it is safe to say that the cardiac patient with an elevated venous pressure and slow circulation time has a high blood volume.

Hypertension. Patients with essential hypertension without congestive failure comprise a group with red cell and total blood volume within normal limits.^{13c, 14} In view of the markedly plethoric appearance of many hypertensives this finding is somewhat surprising and suggests that the practice of phlebotomy for the relief of hypertensive cephalalgia and dizziness cannot be justified on the basis that these symptoms are due to "too much blood."

Diseases of the Thyroid. Plasma, circulating red cell and hence total blood volume are definitely increased in hyperthyroidism¹⁵ and the degree of elevation above normal varies directly with the increase in oxygen consumption as measured by the basal metabolism determination. This increase is less than that seen in congestive heart failure, average increase being about 10 per cent at a basal metabolic rate of $+50$. The effect of iodine in the form of Lugol's solution is to reduce total blood volume and of successful subtotal thyroidectomy to restore total blood volume to within normal limits. The reduction in circulating red cell volume parallels the fall in metabolic rate on therapy.

Blood volume invariably is low in myxedema,¹⁵ the average decrease being about 15 to 20 per cent below normal at a basal metabolic rate of -40 . If anemia is present, the blood volume tends to be lower than the average for myxedema patients without anemia. Administration of thyroid, if successful in raising metabolism, is accompanied by an increase in total volume which returns to normal simultaneously with metabolism.

Nephritis. Total blood volume is below normal in nephritis, the degree of reduction being determined by the extent of the anemia, hypoproteinemia and non-protein nitrogen retention present.¹⁴ Anemia lowers the circulating red cell but tends to increase the plasma volume. Plasma volume varies directly with the total amount of serum albumin present in the blood stream and, therefore, tends to be low when hypoproteinemia is present. As non-protein nitrogen rises, plasma volume increases. Thus, in any phase of the disease total blood volume will reflect the influence of these factors. Since hypoproteinemia usually is more marked in subacute glomerular nephritis with edema (nephrotic syndrome) than in chronic glomerular nephritis without edema, total blood volume usually is more greatly reduced in the former stage of the disease.

In the edematous phase diuresis is accompanied by changes in plasma volume which are not related to the amount of edema lost as measured either by urinary output or weight loss but are determined by the courses of the three factors mentioned above. If therapy raises the serum albumin content of the blood, plasma volume will tend to increase, and if at the same time the circulating red cell volume increases, plasma volume will tend to fall. The relationship of these factors is such, however, that total blood volume always is below normal as long as renal function is depressed regardless of the degree of anemia present. The changes in volume that occur bear no demonstrable relationship to the presence or absence of hypertension.

Parenteral Fluid Administration. Fluids administered intravenously produce marked changes in blood volume. Immediately following the rapid intravenous injection of 50 c.c. of 50 per cent dextrose plasma volume has been observed to increase by 10 per cent or more, returning to normal in about 30 minutes. Altschule and Gilligan¹⁶ followed the course of the plasma volume during and after intravenous infusions of normal saline, hypertonic saline and dextrose solutions in postoperative patients by means of changes in the hematocrit and serum protein concentration and in a few instances by the author's blood volume method. Fifteen hundred cubic centimeters of fluid were given in 30 minutes. The increase in volume was considerable, being as much as 30 per cent when 5 per cent dextrose was used, but less when isotonic saline was given. There was a distinct parallel between the increase in blood volume and the rise in venous pressure. Plasma volume fell to normal in about an hour. When whole blood is given¹⁷ the effect is directly additive, all of the red cells and most of the plasma being retained within the vascular bed.

It appears that considerable caution as to the rate at which intravenous infusions are given is indicated. Rapid injection of hypertonic solutions is an heroic procedure which probably should be reserved for the emergency of shock, pending transfusion.

Anemia. The severity of any anemia commonly is judged by the determination of the hemoglobin concentration, red blood cell count or hematocrit. However, these procedures, even though carried out with the best technics,

can never give any idea of the total quantity of circulating red cells or whole blood in a given case. That the total quantity of blood must be greatly reduced in severe anemia has been appreciated by many authors, but considerable doubt has been expressed as to whether changes in red count or hemoglobin really parallel changes in total blood volume and can be safely used as therapeutic and prognostic guides.^{18, 19}

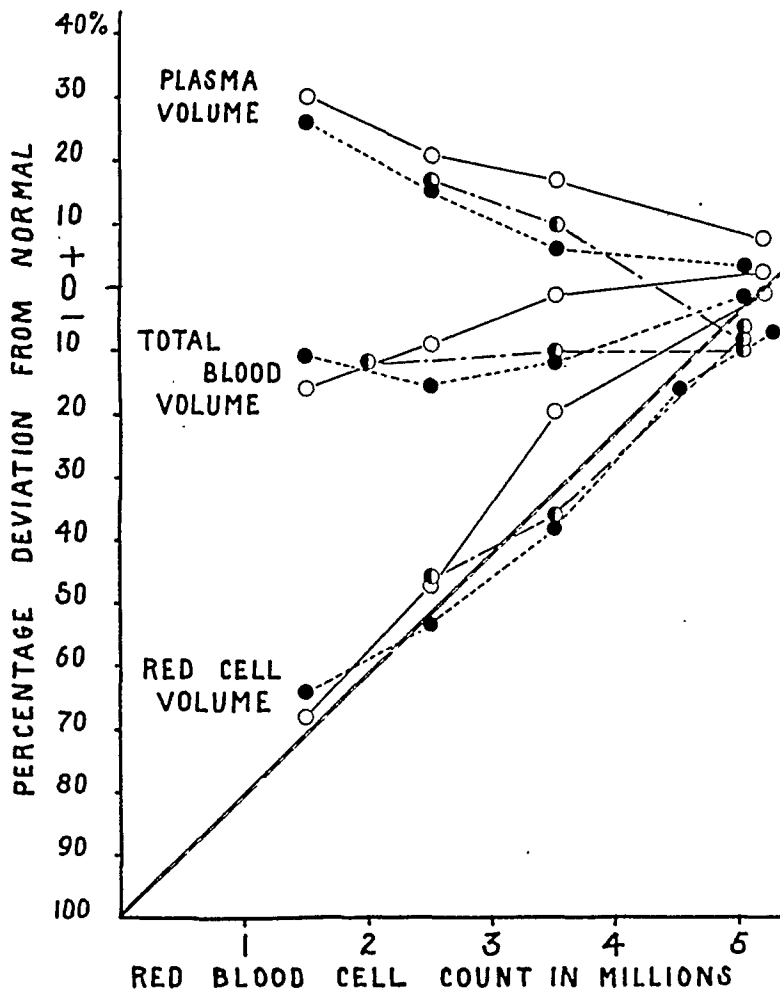


FIG. 2. Plasma, circulating red cell and total blood volume in severe anemia and during recovery. The symbols represent: primary anemia ○; secondary anemia due to all causes ●; and the anemia of nephritis ○. The broken line represents the theoretical direct relationship between red cell count and percentage deviation from normal of the red blood cell volume. (Reproduced by permission from the *Jr. Clin. Invest.*, 1939, xviii, 621-632.)

In the anemic patient the oxygen capacity of a unit quantity of blood is primarily dependent upon the total quantity of hemoglobin, and the severity of anemia should be evaluated in terms of the actual deficit in total circulating hemoglobin rather than the concentration of hemoglobin in a unit quantity of blood. Since total hemoglobin varies within rather narrow limits with the circulating red cell volume, the latter is also a useful criterion.

In anemia plasma volume tends to be above, circulating red cell volume greatly below, and the total blood volume below normal.²⁰ Except that the total blood volume tends to be below normal in chronic nephritis, regardless of the degree of anemia present, the relationship of the blood volume components to each other and to the hematocrit is practically identical in pernicious anemia, hypochromic anemia due to chronic blood loss or of unknown cause and the hemolytic anemias of familial origin, or due to malaria or drug intoxication (figure 2).

In chronic secondary anemia the deficit in circulating red cell volume may be as great as 60 per cent (and even greater in primary anemia) before alarming symptoms of impending collapse appear. During recovery, as the circulating red cell volume rises, plasma volume tends to decrease, so that total blood volume rises slowly and returns to normal only when the circulating red cell volume is fully restored, and the relationship between deficit in circulating red cell volume and hematocrit, red cell count and hemoglobin, illustrated in figure 3, holds true throughout recovery or during relapses. Thus the hematocrit and to a less extent the hemoglobin concentration and red cell count do serve as good indices of the deficit in circulating red cell volume throughout the course of anemia. It is doubtful if they are as reliable immediately following acute hemorrhage or during continued blood loss.

These facts have direct bearing on the matter of transfusion. The purpose of transfusion is not to restore blood volume completely to normal but to supply enough blood to bring a deficient volume up to the point that will tide the patient over in an emergency until his own recuperative powers can be called into play. The extent of return to normal circulating red cell volume desired depends upon whether the patient is to remain at bed rest, is to be subjected to operation, has fever, is in shock, or upon the continuance of bleeding.

From our experience it seems reasonable to assume that a deficit of over 30 per cent in circulating red cell volume constitutes a definite risk under the extreme conditions described above.

In 70 cases of secondary anemia due to all causes the circulating red cell volume was within ± 15 per cent of a line representing a theoretical direct relationship between the percentage of normal circulating red cell volume and the level of the hematocrit, red cell count and hemoglobin (figure 3). Thus, knowing the hematocrit level, it is possible (within these limits) to estimate the percentage of deficit in circulating red cell volume, and knowing the normal circulating red cell volume (figure 1), to calculate the amount of transfused blood needed to raise circulating red cell volume from a critical to a safe level in a given case. Table 1 gives some idea of the amount of red cells lacking at deficits of 60 per cent for males and females with normal total volumes of from 3425 to 6175 c.c. and the amount of whole blood needed to raise the circulating red cell volume from a 60 per cent to a 30 per cent deficit level.

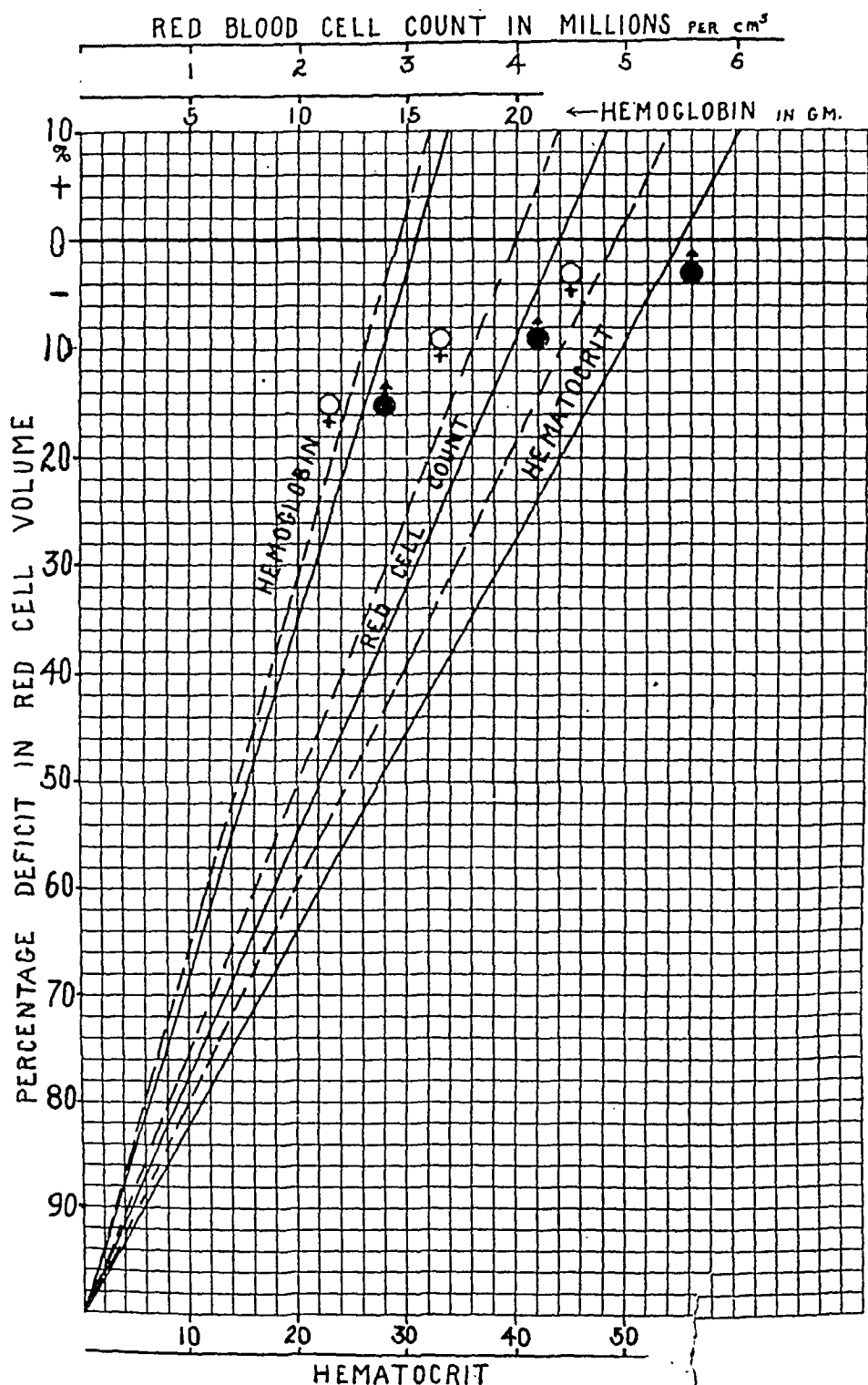


FIG. 3. The relationship between percentage deficit in circulating red blood cell volume to red cell count, hemoglobin and hematocrit at various levels of anemia. (Reproduced by permission from the *Jr. Clin. Invest.*, 1939, xviii, 621-632.)

Thus, while a 500 c.c. transfusion may tide over a small person at rest, it may be of little value under the stress of operation, and it is evident that in larger persons, particularly males, a full liter or more may be required. It is highly probable that the unexpected and sudden peripheral vascular collapse frequently encountered post-operatively, or in burns, or in the toxemia of pregnancy is due in great part to failure to transfuse enough blood.

TABLE I

The Deficit in Circulating Red Cell Volume at Critical Levels of Anemia and the Transfusion Requirement for Males and Females

Height cm.	Sex	Normal Total Blood Volume c.c.	Deficit of 60% in Cir- culating Red Cell Volume * c.c.	Transfusion Requirement to De- crease Deficit to 30% †	
				Red Cells c.c.	Whole Blood ‡ c.c.
150	F.	3425	822	411	683
155	F.	3750	900	450	750
155	M.	3775	996	498	830
160	F.	3900	936	468	780
160	M.	4550	1200	600	1000
165	F.	4050	972	486	810
165	M.	4975	1313	657	1095
170	F.	4150	996	498	830
170	M.	5325	1405	703	1172
175	F.	4200	1008	504	840
175	M.	5550	1465	737	1228
180	M.	5700	1504	750	1253
185	M.	5850	1544	772	1287
190	M.	6000	1584	792	1320
195	M.	6175	1630	815	1358

* Hematocrit level of about 20.

† Hematocrit level of about 37.

‡ Assuming hematocrit of transfusion blood about 40.

Polycythemia Vera. It is well known that total blood volume is greatly above normal in this disease. As a rule, plasma volume is normal, the increase being due entirely to the huge quantity of circulating red cells.^{18, 20} This increase in terms of percentage elevation above normal circulating red cell volume bears a fairly direct relationship to the hematocrit level. Plasma volume is little changed after phlebotomy, but red cell volume comes down. In our experience the most reasonable form of treatment seems to be repeated phlebotomy, the desired hematocrit level to maintain being between 40 and 50, at which most patients remain fairly symptom free.

Pregnancy. Dieckmann et al.²¹ found some elevation in blood volume during the first and second trimester of pregnancy due chiefly to an hydremia, and an increased water content of the blood has been noted by Feldman et al.²² A complete study of the changes in blood volume throughout normal pregnancy and during the puerperium has been made by Thomson et al.²³ There is a progressive increase above normal in plasma and total blood volume beginning early in pregnancy and reaching a maximum during the ninth lunar month, after which a definite decrease occurs fairly

rapidly. Thus, an increase in total blood volume amounting to almost 50 per cent at the peak has fallen to about 10 per cent above normal at term. The circulating red cell volume also increases but proportionately less than does the plasma volume, so that hematocrit, hemoglobin, and red cell count all progressively decline up to the ninth lunar month even though total blood volume is highest at this time. Total volume is essentially normal in uneventful cases 10 days after delivery.

The course of the blood volume in a group of women who had proved valvular heart disease but who went through pregnancy without any evidence of decompensation was similar to the normal group.²⁴

Three facts of importance stand out. (1) The period of greatest increase in blood volume coincides with the period of greatest incidence of heart failure in pregnancy,²⁵ and this plethora has undoubted significance in the management of heart failure. (2) The "anemia of pregnancy" is not a true red cell deficiency but the result of hydremia. Unless the mean corpuscular hemoglobin concentration is low, it is doubtful whether any alarm need be felt or antianemic therapy used even when the hematocrit falls as low as 30. (3) Total blood volume is on an average only about 500 c.c. above normal at the onset of labor. A hemorrhage of a liter may constitute as serious an emergency on the delivery table as in the accident ward.

Anesthesia and Surgical Operations. Blood losses at operation have been carefully measured,^{26, 27} and it is well known that in a normal person the amount of blood lost even in long major operations rarely is sufficient to precipitate shock. During the induction of anesthesia plasma volume tends to be diminished slightly.²⁸ During operation plasma volume fluctuates somewhat, there being a general tendency for it to increase as systolic pressure falls and decrease as it rises, but as a rule plasma volume is reduced from 10 to 20 per cent at the end of uneventful operations. In normal persons this reduction may be somewhat offset by an increase in the circulating red cell volume so that total blood volume may be only slightly reduced. It is probable, however, that in acute or chronic anemias no considerable reserve of red cells exists.

Severe reductions in plasma and total volume have been observed to take place during recovery from anesthesia in the "ether bed," exceeding the amounts lost at the end of operation. These losses are due to sweating and lay stress on adequate fluid replacement during recovery.

Fever. In fever induced by intravenous injection of typhoid vaccine no significant changes in total or red cell volume take place. Plasma volume may fall from 5 to 10 per cent as temperature rises but shortly afterwards is restored and remains essentially normal.²⁹ In recent years much attention has been given "artificial" fever. When body temperature is raised by exposure to radiant energy in any form, since the thermo-regulating mechanism remains unaffected, the mechanism increasing heat dissipation is called into play in the effort to maintain normal temperature. The peripheral

vascular bed becomes widely dilated, blood flow speeds up, blood is diverted to the skin capillaries and quantities of sweat are poured out to increase evaporative loss. Since the circulating plasma volume is determined by the rate of loss from, and absorption of fluid into the blood stream, the induction of artificial fever is attended invariably by some reduction in plasma and total volume. This reduction may be extreme (30 to 35 per cent) and precipitate peripheral vascular collapse, leading to coma and even death unless fluids are given adequately by mouth or vein.

Shock. Perhaps no other condition has been studied so extensively as shock, and it is now commonly accepted that in shock, whether "traumatic," "surgical" or "medical," the effective circulating blood volume is always reduced. The cause of the initial decline in volume, and whether in the absence of hemorrhage the quantity of blood so lost to the circulation is "pooled" in viscera or has actually escaped from the vascular bed remain questions as yet unanswered. The relationship between the degree of lowering in blood volume and the level of systolic blood pressure is another debatable question.

A review of the voluminous literature on shock is beyond the scope of this paper, but certain experimental observations may throw some light on these questions. Keeley et al.³⁰ produced experimental shock in anesthetized dogs by severe burns. Immediately after the burn a large reduction in plasma volume took place, and it was demonstrated that all of this fluid was lost into the burned area. On continued observation plasma volume continued to decrease gradually, but a considerable increase in circulating red cell volume occurred so that the total volume declined less than the plasma. Systolic pressure remained normal, although accompanied by increasingly rapid pulse and respiratory rate, until total blood volume was reduced about 30 per cent, when the systolic pressure suddenly fell sharply and the animal succumbed shortly thereafter. This decline in volume was accompanied by a lowering of both arterial and venous oxygen saturation, probably to be accounted for by hemoconcentration, slow blood flow due to viscosity and diminished cardiac output, the effect of acidosis on oxygen take-up in the lungs and the influence of the low CO₂ tension, resulting from acidosis, on oxygen release.

Postmortem examination of these animals revealed no evidence of "pooling." The entire gastrointestinal tract was markedly ischemic, and there had been no intestinal hemorrhage. Liver and spleen were firm and contained little blood. Lungs were dry and slightly congested. The entire body appeared dehydrated and relatively bloodless. These animals were given no fluids, and evaporation loss from the lungs was considerable.

More recent studies³¹ on the effect of various types of intravenous replacement fluids in these shock preparations have shown that the administration of normal saline, hypertonic glucose, plasma or whole blood, even though they temporarily increased the blood volume with a resultant rise

in systolic pressure, did not prevent eventual collapse; if given after any considerable fall in systolic pressure had occurred. Plasma is the most effective replacement fluid, being longest retained, and decreasing the hemoconcentration and restoring the pH of the blood far better than blood or normal saline.

Other workers³² have followed the course of blood volume in relation to peripheral flow, skin temperature and other hemodynamic measurements in patients in the terminal phase of infectious and degenerative disease. In each instance a marked decrease in plasma and total blood volume definitely preceded the eventual fall in blood pressure. Many of these patients developed peripheral edema terminally.

In shock there is first a rapid and considerable loss of plasma either into the site of injury or in a widespread manner from capillary beds. The immediate effect is hemoconcentration, slowed peripheral blood flow and decreased filling of the right heart, accompanied by vasoconstriction in the effort to maintain circulation. This vasoconstriction has the effect of maintaining systolic pressure even with a markedly reduced volume. If at this point volume is restored, recovery may take place, but if circulation remains inadequate and oxygen exchange is further interfered with, a further reduction in plasma volume may be expected due to widespread alterations in capillary permeability brought about by anoxia, and the vicious cycle so established is potentially fatal. It is, therefore, evident that the low systolic pressure clinically "characteristic" of shock is to be interpreted not as "compensatory" mechanism but as a more or less complete breakdown of compensation.

SUMMARY

An attempt has been made to clarify certain misconceptions as to the state of the blood volume in health and disease arising from conflicting reports in the literature. No conclusions have been drawn as to the causes of changes in volume that occur in pathologic states. The characteristic behavior of the blood volume observed in normals and during various phases of congestive heart failure, essential hypertension, hyperthyroidism and myxedema, nephritis, primary and secondary anemia, polycythemia and in shock has been commented on. A method of calculating required transfusion amounts for the individual on the basis of predicted normal blood volume and level of anemia has been described. Appreciation of these states and changes may offer the clinician a sounder basis for the evaluation of diagnostic and therapeutic procedures in the conditions studied.

The author wishes to express his gratitude to Dr. Henry A. Christian whose interest in the blood volume initiated, and whose friendly encouragement has aided many of the studies herein described; and to my associates in this work: Prof. M. I. Gregersen, Dr. Wm. A. Evans, Jr., Dr. E. A. Stead, Jr., Dr. Alfred W. Harris and many others.

REFERENCES

1. KEITH, N. M., ROWNTREE, L. G., and GERAGHTY, J. T.: A method for the determination of plasma and blood volume, *Arch. Int. Med.*, 1915, xvi, 547.
2. HOOPER, C. W., SMITH, H. P., BELT, A. E., and WHIPPLE, G. H.: Blood volume studies. I. Experimental control of a dye blood volume method, *Am. Jr. Physiol.*, 1920, li, 205.
3. SMITH, H. P.: Blood volume studies. II. Repeated determination of blood volume at short intervals by means of the dye method, *Am. Jr. Physiol.*, 1920, li, 221.
4. GRIESBACH, W.: Eine klinisch brauchbare Methode der Blutmengenbestimmung, *Deutsch. med. Wchnschr.*, 1921, xlvii, 1289.
5. SEYDERHELM, R., and LAMPE, W.: Die Blutmengenbestimmung und ihre klinische Bedeutung. Unter besonderer Berücksichtigung der Farbstoffmethode, *Ergebn. d. inn. Med. u. Kinderh.*, 1925, xxvii, 245.
6. WOLLHEIM, E.: Die Bestimmung der zirkulierende Blutmenge, *Ztschr. f. klin. Med.*, 1928, cviii, 463.
7. HEILMEYER, L.: Das Verhalten des Kongorots zu den Serumkolloiden, zugleich ein methodischer Beitrag zur Blutmengenbestimmung mit Kongorot nach Griesbach, *Biochem. Ztschr.*, 1929, ccxii, 430.
8. GRAFF, S., and CLARKE, H. T.: Determination of plasma volume. I. The dye method, *Arch. Int. Med.*, 1931, xlviii, 808.
9. UHLENBRUCK, P., and LEYENDECKER, T.: Stufenphotometrische Blut-Plasamengenbestimmungen bei Herzkranken, Normalpersonen und nach sportlichen Anstrengungen, *Ztschr. f. klin. Med.*, 1931, cxviii, 164.
10. BROCKMANN, H.: Ein Beitrag zur Frage der Bestimmung der zirkulierenden Blutmenge beim normalen lebenden Menschen mit der Farbstoff-Injektionsmethode, unter Benutzung des Pulfrichschen Stufenphotometers, *Ztschr. f. d. ges. exper. Med.*, 1933, lxxxvii, 208.
11. SUNDERMAN, F. W.: The measurement of serum volume, *Jr. Biol. Chem. (Proc.)*, 1935, cix, xci.
12. GREGERSEN, M. I., GIBSON, J. J., and STEAD, E. A.: Plasma volume determination with dyes, errors in colorimetry; use of the blue dye T-1824, *Am. Jr. Physiol.*, (Proc.) 1935, cxiii, 54.
- 13a. GIBSON, J. G., 2ND, and EVANS, WM. A., JR.: Clinical studies of the blood volume. I. Clinical application of a method employing the azo dye "Evans Blue" and the spectrophotometer, *Jr. Clin. Invest.*, 1937, xvi, 301.
- 13b. GIBSON, J. G., 2ND, and EVANS, WM. A., JR.: Clinical studies of the blood volume. II. The relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans, *Jr. Clin. Invest.*, 1937, xvi, 317.
- 13c. GIBSON, J. G., 2ND, and EVANS, WM. A., JR.: Clinical studies of the blood volume. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure, *Jr. Clin. Invest.*, 1937, xvi, 851.
14. HARRIS, A. W., and GIBSON, J. G., 2ND: Clinical studies of the blood volume. VII. Changes in blood volume in Bright's disease with or without edema, renal insufficiency, or congestive heart failure, and in hypertension, *Jr. Clin. Invest.*, 1939, xviii, 527.
15. GIBSON, J. G., 2ND, and HARRIS, A. W.: Clinical studies of the blood volume. V. Hyperthyroidism and myxedema, *Jr. Clin. Invest.*, 1939, xviii, 59.
16. ALTSCHULE, M., and GILLIGAN, D. R.: The effect on the cardiovascular system of fluids administered intravenously in man. I. Studies of the amount and duration of blood volume changes, *Jr. Clin. Invest.*, 1938, xvii, 401.
17. GIBSON, J. G., 2ND: Unpublished observations.
18. HADEN, R. L.: The red cell mass in polycythemia in relation to diagnosis and treatment, *Am. Jr. Med. Sci.*, 1938, cxcvi, 493.

19. BENNETT, T. I., DOW, J., LANDER, F. P. L., and WRIGHT, S.: Severe hemorrhage from stomach and duodenum, *Lancet*, 1938, ii, 651.
20. GIBSON, J. G., 2ND, HARRIS, A. W., and SWIGERT, V. W.: Clinical studies of the blood volume. VIII. Macrocytic and hypochromic anemias due to chronic blood loss, hemolysis and miscellaneous causes, and polycythemia vera, *Jr. Clin. Invest.*, 1939, xviii, 621.
21. DIECKMANN, W. J., and WEGNER, C. R.: Blood in normal pregnancy; blood and plasma volumes, *Arch. Int. Med.*, 1934, liii, 71.
22. FELDMAN, H., VAN DONK, E. C., STEENBOCK, H., and SCHNEIDERS, E. F.: Hydremia as factor in anemia of pregnancy, *Am. Jr. Physiol.*, 1936, cxv, 69.
23. THOMSON, K. J., HIRSHEIMER, A., and EVANS, W. A., JR.: Studies on the circulation in pregnancy. III. Blood volume changes in normal pregnant women, *Am. Jr. Obst. and Gynec.*, 1938, xxxvi, 48.
24. THOMSON, K. J.: Personal communication.
25. CARR, F. B., and HAMILTON, B. E.: Five hundred women with serious heart diseases followed through pregnancy and delivery, *Am. Jr. Obst. and Gynec.*, 1933, xxvi, 824.
26. GATCH, W. D., and LITTLE, W. D.: Amount of blood lost during some of the more common operations, *Jr. Am. Med. Assoc.*, 1924, lxxxiii, 1075.
27. PILCHER, F., JR., and SHEARD, C.: Measurements on loss of blood during transurethral prostatic resection, etc., *Proc. Staff Meet. Mayo Clin.*, 1937, xii, 209.
28. GIBSON, J. G., 2ND, and BRANCH, C. D.: Blood volume changes during surgical procedures, *Surg., Gynec. and Obst.*, 1937, lxxv, 1.
29. GIBSON, J. G., 2ND, and KOPP, I.: Studies in the physiology of artificial fever. I. Changes in the blood volume and water balance, *Jr. Clin. Invest.*, 1938, xvii, 219.
30. KEELEY, J. L., GIBSON, J. G., 2ND, and PRJOAN, M.: The effect of thermal trauma on blood volume, serum protein, and certain blood electrolytes: An experimental study of the effect of burns, *Surgery*, 1939, v, 872.
31. DUNPHY, J. E., GIBSON, J. G., 2ND, and KEELEY, J. L.: Observations on the pathology of experimental traumatic shock, *Surg., Gynec. and Obst.* (In press.)
32. STEAD, E. A., JR.: Personal communication.

ACUTE OCCLUSIONS OF THE PERIPHERAL ARTERIES; CLINICAL ANALYSIS AND TREATMENT*

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No more dramatic episode exists in medicine, than the sudden onset of an arterial occlusion. In fact, the onset is so characteristic that the condition is seldom overlooked. Unfortunately, however, the proper therapy is often too long delayed.

I am therefore presenting an analysis of 31 cases † of acute closure of the peripheral arteries to call attention to certain clinical features that require emphasis, and to show that extremities can be saved when proper conservative measures are instituted. I shall also attempt to show that the loss of life in individuals who are properly treated is not due to the acute arterial lesion per se, but rather to the basic disease that existed before the embolism or thrombosis occurred. If one can prevent the formation of gangrene, the chances of saving the affected limb and thereby prolonging life are proportionately greater.

GENERAL CONSIDERATIONS

An acute occlusion of a peripheral artery consists either of an embolism or a thrombosis. An analysis of the numerous causes of these conditions would constitute an essay in itself, and is outside the scope of this paper. Suffice it to say, that there are very definite criteria to determine whether one is dealing with an embolism or a thrombosis.

When a sudden arterial obstruction occurs in a patient who shows evidence of peripheral vascular disease and who presents no signs of a focus from which emboli might originate, that obstruction is considered thrombotic in nature. On the other hand, when an acute closure of an arterial pathway takes place in an individual who presents no evidence of peripheral vascular disease, but exhibits definite signs of cardiac disease, that closure may be diagnosed as embolic, particularly so, when the individual is in the younger age group.

Heart conditions of particular importance in the diagnosis of embolism are: (1) auricular fibrillation, (2) mitral stenosis, (3) acute or subacute bacterial endocarditis, (4) infarction of the wall of the left ventricle with thrombus formation, and (5) paradoxical embolism with patent foramen ovale. Pulmonary phlebitis in lung infections is another predisposing cause

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† Twenty-seven patients are from the private and ward services of the Bronx Hospital and four are from the author's private practice, outside the hospital.

of embolism. An embolus may also arise from a thrombosis of the wall of another artery, or from an aneurysm above the site of lodgement.

It is important to remember that emboli are seldom large enough to occlude the larger arteries, such as the aorta and common iliacs, except perhaps at the bifurcation of these vessels, where the lumen is suddenly narrowed, and a saddleback anatomic arrangement exists. In arteriosclerotic arteries, partial or complete thrombosis occurs when the atheromatous intima ulcerates through, and emboli may be caught at that particular point; so that even with an embolic background, the real etiology of sudden closure at any point of an artery may be thrombotic in character.

ETIOLOGY

Age. There were 13 cases diagnosed as embolism. Two were 25 and 28 years old respectively, four were between 40 and 50, and seven over 50 years of age. Of the 18 cases diagnosed as thrombosis, one was 47 years of age, six were between 50 and 60, and eleven were over 60 years of age. The embolic group therefore, was definitely younger. There was no difference in the age of either sex in the embolic or thrombotic group.

Sex. The embolic group compromised five male and eight female patients. The thrombotic group had an equal number of each sex. Sex, therefore, was no factor in etiology.

Diabetes. In the embolic group there were four patients with diabetes, all four being females. In the thrombotic patients, 10 had diabetes, three males and seven females. It seems therefore, that diabetes prevailed more in females than in males, 11 out of 14 diabetics being females.

Fibrillation. Nine cases of embolism had fibrillation. Eight of these definitely fibrillated prior to the acute accident. In one case, no mention was made as to the time of onset of fibrillation. Of the 18 thrombotic cases, seven presented signs of fibrillation, five definitely before, and one after the accident. In one instance the time of onset of fibrillation could not be determined. In the embolic group, therefore, fibrillation was present before the accident in 61 per cent of the cases, and in the thrombotic group in only 28 per cent of patients.

UNDERLYING DISEASE STATUS

Embolism. The two patients who were 25 and 28 years old, had sub-acute and acute bacterial endocarditis, respectively. One patient had coronary thrombosis, one had arteriosclerotic heart disease, three had hypertensive heart disease, and six had rheumatic heart disease.

Thrombosis. One patient had coronary thrombosis, four had hypertensive heart disease, six had arteriosclerotic heart disease, three had rheumatic heart disease, and four had arteriosclerosis obliterans. From these data it may be seen that the most frequently associated condition in the majority of cases was heart disease; and as will be seen later, it was this

condition, and not the peripheral vascular state, that determined whether the patient survived.

ANATOMICAL CONSIDERATIONS

Vessels Involved. The aortic bifurcation was involved in two patients, once in embolism and once in thrombosis. The external iliac vessels were affected in five cases, once in embolism and four times in thrombosis. The femorals were occluded in eight cases, five times in embolism and three times in thrombosis. The popliteal was involved in ten cases, four times in embolism and six times in thrombosis. The anterior tibial was occluded in three instances, all being thrombosis. There was one thrombosis of the axillary artery, one embolism of the small vessels of the hand, and one embolus to the digitals of the big toes. There was really no specificity of vessel involvement either in embolism or thrombosis.

Multiple Arterial Involvements. There were four cases of embolism with multiple arterial occlusions and only one case of thrombosis with more than one simultaneous arterial obstruction.

Onset of Gangrene. In only eight of the 13 cases of gangrene could the date of onset of gangrene be determined. The one case of aortic bifurcation obstruction developed gangrene of the thighs, legs and feet in 24 hours. Two cases of external iliac artery occlusion developed gangrene in two and 15 days respectively. Gangrene set in from one day to three weeks in four cases of femoral obstruction, while one case of embolism to the digitals of the big toe showed gangrene in 24 hours.

Vessels involved in cases of gangrene were the aortic bifurcation in one case, the external iliac in two cases, the femoral in seven cases, the popliteal in two cases, and the digitals to the toes in one case. It seems, therefore, that the femoral artery occlusion produced gangrene most frequently, but one must remember that six of these seven cases were treated prior to the onset of gangrene by individuals not trained in the conservative therapy of acute occlusions.

SYMPTOMS

The symptoms of an acute obstruction to the arterial supply of a limb come on suddenly, and no differentiation between embolism and acute thrombosis can be made from the symptoms alone. The first symptom in 23 of the 31 cases (76 per cent), was a sudden onset of sharp pain in the affected limb. It was present in eight of the embolic and 15 of the thrombotic cases. Six cases complained of a sudden onset of numbness (four embolic and two thrombotic). One patient with thrombosis had a gradual onset of pain, and one patient with embolism complained at first of "pins and needles" sensation. Other symptoms followed rapidly in order: sudden pallor with grayish cyanosis in severe cases; coldness of the limb; loss of sensation and motion of the distal part of the extremity.

SIGNS

The extremity was pale or gray cyanotic in color; felt cold, below the site of obstruction; the superficial veins were collapsed; sensation in the distal part of the limb was diminished or lost; and in high occlusions, the function of the distal joints was lost. The pulsations of the main arterial vessels were absent, at least below the site of occlusion. Often for a period of hours, days, or weeks, the pulsations of vessels proximal to the affected area were also absent. This loss of pulsation occasionally extended to the opposite member, and was due to the associated reflex vasomotor spasm.

LABORATORY FINDINGS

The evaluation of fever, white blood count with differential, and sedimentation time was difficult, due to the fact that the majority of patients had preëxisting cardiac failure, polycythemia, or infection. Often too, the case was admitted weeks after the acute closure and the findings were therefore of no importance.

LIST OF CASES

Acute Occlusions of the Peripheral Arteries

Case	Age	Sex	Diagnosis	Complications	Dia- betes	Ther- apy	Gan- grene	Am- pu- ta- tion	Died after Accident	Living
62731	25	F.	E. R. Fem.	R.H.D., Sub. B.	0	0	2 da.	0	16 days	
75317	61	F.	E. R. Fem.	H.H.D.	+	0	1 da.	+	3 mos. after discharge	
58865	50	F.	E. L. Pop.	R.H.D., A.F.	0	0	16 da.	+	?	?
49840	50	F.	E. R. Fem., R. Brach.	H.H.D., A.F.	+	0	1 da.	0	10 days	
61974	64	M.	T. R. Fem.	A.S.H.D.	0	0	2 wks.	+	?	?
62216	60	F.	T. R. Fem.	A.S.H.D., A.F.	+	0	in 3 wks.	+	?	?
60229	63	F.	T. R. Pop.	Cor. Thromb.	+	0	6 da.	+	30 mos. after discharge	
36801	73	F.	T. L. Fem.	H.H.D., A.F.	0	0	1 da.	0	2 days	
97686	41	M.	E. R. and L. Pop.	R.H.D., A.F.	0	Pavaex	0	0		11 mos.
75457	28	M.	E. L. Pop.	R.H.D., Ac. Bact.	0	Pavaex	0	0	10 days	
97813	46	M.	E. L. Fem., R. Ulnar	R.H.D., A.F.	0	Pavaex	0	0		10 mos.
102949	46	M.	E. R. Pop.	R.H.D., A.F.	0	Pavaex	0	0		5 mos.
84300	56	F.	E. L. Fem.	R.H.D., A.F.	+	Pavaex	23 da.	0	26 mos. after discharge	
75752	60	F.	E. Digitals to toes	H.H.D., A.F.	0	Pavaex	1 da.	0		33 mos.
88805	67	F.	E. R. Pop., L. Ant. Tib.	A.S.H.D., A.F., H.H.D.	0	Pavaex	0	0	5 days	

E. refers to embolism, T. to thrombosis, R.H.D. to rheumatic heart disease, H.H.D. to hypertensive heart disease, A.S.H.D. to arteriosclerotic heart disease, A.S.O. to arteriosclerosis obliterans, A.F. to auricular fibrillation.

These cases are brought up to date as of December 30, 1939.

LIST OF CASES (*Continued*)

Case	Age	Sex	Diagnosis	Complications	Dia- betes	Ther- apy	Gan- grene	Am- puta- tion	Died after Accident	Living
M. R. Dr. F.	55	F.	E. L. Ext. Iliac	R.H.D., A.F.	+	Pavaex	0	0	4 days	
S. S. Dr. W.	46	M.	Bifur. E. Aorta	Cor. Thromb.	0	0	1 da.	0	4 days	
103387	47	F.	T. Bifur. Aorta	R.H.D., A.F.	0	Pavaex	0	0	16 da. after discharge	
104101	61	M.	T. L. Ext. Iliac	A.S.O.	0	Pavaex	0	0		4 mos.
105918	56	F.	T. R. Pop.	R.H.D., A.F.	+	Pavaex	0	0		2 mos.
106857	53	M.	T. Ant. Tib.	A.S.H.D.	0	Pavaex	0	0		1 week
82403	67	F.	T. L. Pop.	A.S.H.D., H.H.D.	+	Pavaex	0	0	?	?
91909	68	M.	T. L. Ext. Iliac	A.S.O.	+	Pavaex	0	0		17 mos.
Dr. A. I.	51	M.	T. L. Ext. Iliac	A.S.O.	0	Pavaex	2 da.	+		8 mos.
98872	52	M.	T. Small vessel R. hand	A.S.H.D., A.F., H.H.D.	+	Pavaex	0	0	18 days	
96367	70	M.	T. L. Ant. Tibial	Polycythemia, Chr. Bronchitis	+	Pavaex	0	0		13 mos.
C. A. Dr. Kohlen- berg	65	M.	T. R. Axil- lary	A.S.H.D., Nephritis	0	0	0	0	12 days	
103686	64	F.	T. R. Ext. Iliac	A.S.H.D., A.F., A.S.O.	+	0	15 da.	0		4 mos.
93712	66	F.	T. R. Fem., L. Pop.	A.S.H.D.	+	Pavaex	0	0	3 days	
92860	57	F.	T. R. Ant. Tibial	R.H.D., A.F.	+	Pavaex	0	0		16 mos.
71283	52	M.	T. R. Pop.	A.S.H.D.	0	Pavaex	0	0	33 mos. after discharge	

The blood Wassermann and Kahn tests were done in 21 patients and all proved negative.

No oscillometric tracings were taken for fear of further trauma to the damaged peripheral vascular system.

In nine cases tested by means of thermal reflex vasodilatation¹ the affected limb gave little or no response. The reaction in the opposite limb depended on the state of the peripheral circulation.

Intra-arterial diodrast injections were done in several cases, and the block was demonstrated, but no conclusions were drawn from this procedure. (The reason for this is that the mere insertion of a needle into an artery may produce a spasm of the vessel, and only when patency of the vascular system is visualized, can the result of this procedure be accepted without hesitancy.)

CONSERVATIVE THERAPY

The conservative therapy of acute arterial occlusions by the use of alternate suction and pressure was reported by Herrmann and Reid² in

1933. Landis and Gibbon³ in the same year also showed the effects of this form of treatment on the blood flow to the lower extremities. Linton⁴ in 1937 reported 60 per cent successful results in sudden arterial closures by the use of "pavaex." His results compared more than favorably with those of embolectomy published by Lund.⁵ Linton divided 44 cases of acute arterial occlusions into three groups in order to evaluate the effect of different forms of treatment. In the group which received no therapy, the limb was saved in 29 per cent of the cases. In the group treated by embolectomy a similar successful result was obtained in 33 per cent. Suction pressure therapy was used in the last group and the limb affected was saved in 60 per cent of the cases. In 1932 Cook and Brown⁶ measured the vasodilating effects of alcohol on the peripheral arteries, while de Takats⁷ in 1936 emphasized the value of papaverine, intravenously, to allay the pain and arterial spasm incidental to acute closures.

In the conservatively treated cases of this series, I used a combination of the foregoing measures, and adhered to the following routine. The patient was put to bed and was given one-half grain of papaverine intravenously as soon as possible. He was covered with wool blankets; warm water bottles were placed in the axillae when the lesion was in the lower extremities; and whiskey was given in one ounce doses, three times daily.

The patient was seen by a member of the peripheral vascular department as soon as possible, and the affected limb was placed in a suction pressure apparatus. The apparatus was adjusted so that during the negative phase, the skin of the limb would either become pink, or the superficial veins would fill: during the positive phase the skin of the extremity would pale, or the superficial veins would collapse. If the patient could stand it, he would receive six to twelve hours of continuous treatment. On the second day he would receive four to six hours, and then the treatment would gradually be reduced to two hours daily. We tried in most cases to give a minimum of 100 treatment hours.

The contraindications to the use of suction pressure therapy are, first, pain during therapy; second, infection; and third, edema. Our treated cases presented neither infection nor edema, and in only one instance was pain during treatment a factor in the cessation of therapy. It was usually high negative pressure that caused pain and the negative pressure could often be diminished to the point where treatment could be tolerated.

RESULTS OF TREATMENT

In discussing the results of treatment, I shall divide this series into the untreated and the conservatively treated groups. The untreated group comprised eight cases seen between October 1933, and July 1936. There were four embolic and four thrombotic patients. Of the four embolic cases, all developed gangrene. The femoral artery was affected in three instances, one of which was amputated at mid-thigh. All three died in ten days to

three months. The fourth case, involving the popliteal artery, was amputated at mid-thigh, left the hospital alive, but no follow-up was obtained. In the four cases of thrombosis, all developed gangrene. The femoral artery was affected in three instances, two of which were amputated at mid-thigh. The two amputated cases left the hospital and no follow-up was obtained. The third femoral artery case died in two days. The popliteal artery was involved in the fourth case. This patient had a mid-thigh amputation, and died two and one-half years after discharge from the hospital.

Of the eight cases, therefore, all had gangrene, and five were amputated. Of the five amputated cases, three could not be followed, one died three months after discharge, and one died two and one-half years after discharge. The three non-amputated cases died in two to 19 days.

Of 23 cases treated conservatively since July 1936, there were nine embolic and fourteen thrombotic patients.

Of the nine embolic cases eight were treated with suction pressure therapy. These comprised occlusions of two femorals, four popliteals, one external iliac, and one case of the digitals to the toes. There were only two instances of gangrene, and in no case was it necessary to amputate. Four patients are alive after five to 33 months; three patients died of cardiac failure in four to ten days after the accident. The eighth patient was discharged from the hospital and died 31 months later. The ninth case, that of the patient who did not receive pavaex therapy, was an instance of coronary thrombosis followed by arterial obstruction at the aortic bifurcation. He had been treated outside the hospital with a heat lamp, and had developed extensive gangrene. This patient died four days after the accident.

Of the 14 thrombotic cases, 12 were treated with suction pressure therapy. These comprised one case of obstruction of the aortic bifurcation, one of the femoral, three of the external iliac, three of the popliteal, three of the anterior tibial, and one of the small vessels of the hand. There was only one instance of gangrene, and this occurred in an external iliac involvement. This was the only case necessitating a mid-thigh amputation. The two cases not treated by suction pressure therapy were: (1) a thrombosis of the axillary artery, and (2) a thrombosis of the external iliac artery. The former did not develop gangrene, but the case died 12 days after the accident. The latter patient, still alive, had developed moist, gangrenous lesions of the toes, and so suction pressure therapy was contraindicated.

Of the 12 patients treated with suction and pressure, seven are alive; (six are alive after four to 17 months; one is a recent anterior tibial lesion of one week's duration, and is doing well); three died four days to 33 months after leaving the hospital; one died in three days while in the hospital, and one could not be followed up after discharge. Including the two cases not treated with suction pressure therapy, there are eight known living, five known dead, and one with no follow-up.

Of the entire 23 cases, therefore, five developed gangrene, but there was only one amputation. Eleven patients are known to be alive after four to 33 months, and one is alive one week after the accident and is doing well. Ten are known dead, and in one there was no follow-up. There was no essential difference between the results in the embolic and those in the thrombotic patients.

In comparing the data of the untreated and conservatively treated groups, it is only fair to omit three cases from the conservative series: those involving the axillary, the small vessels of the hand, and the digitals to the toes. The results in untreated cases then give the following figures: a loss of limb in 62.5 per cent of the cases, and a known mortality of 62.5 per cent. In cases conservatively treated there was loss of limb in only 5 per cent (one case) and a mortality rate of 40 per cent.

STAY IN HOSPITAL

The length of stay in the hospital in the cases of this series was dated from the time of admission to the time of discharge if the arterial lesion was present on admission. Otherwise it was dated from the day the accident occurred on the ward to the time of discharge. In the eight cases of the untreated series, the length of stay was two to 60 days, with an average of 32.4 days; and in the amputated patients an average of 45.8 days. In the conservative treatment series, the length of stay for the embolic group was 26.2 days, and for the thrombotic group 24.1 days, an average of 25 days. For the suction pressure group the average hospital stay was 25 days, an average of seven days less than that of the untreated group, and 20 days less than the amputated group.

TIME OF ONSET OF THERAPY

In the 16 patients who did not develop gangrene, pavaex therapy was instituted from two hours to five days after the accident, and in one case, 21 days after the occlusion. In the three cases where gangrene set in, therapy was started 15 to 72 hours after the obstruction occurred. In the four cases that died in the hospital, treatment was started in eight to 16 hours after the occlusion, so that in this series the actual time of onset of pavaex therapy was not the deciding factor as to whether the patient would live, or gangrene set in.

TOTAL HOURS OF TREATMENT

In the 16 of the 18 cases that survived hospital stay, the number of treatment hours with suction pressure therapy was from four to 160. The period of treatment varied according to the state of the limb, the restlessness of the patient, and the demand of the bed by the hospital. Pain was relieved almost immediately in the majority of cases with the use of suction pressure therapy. Function of the distal parts returned about 24 to 48 hours in the

popliteal cases. In one external iliac case, there was a loss of function of the ankle (this was the case that was amputated in two weeks due to gangrene). In one femoral case there was a permanent loss of function of the big toe. Sensation returned at the same time as function. Warmth of the limb returned considerably later, sometimes in weeks and sometimes not at all.

RETURN OF PULSATIONS

A consideration of this phenomenon entails the evaluation of reflex vasospasm. It is a known fact that when a lesion occurs in an artery (or vein), a spasm may occur in that vessel, proximal to the site of the lesion. This spasm may extend for varying distances up the vessel, and may extend even to the vessels of the opposite limb. In the case of the lesion of a small artery to the hand, no pulsations could be felt in the entire upper extremity of the involved side. Nine hours after the accident the brachial pulsation could be felt. The radial artery pulsation returned in three days, but the ulnar could never be felt. Palpable pulsations returned in six other cases; the case of partial thrombosis of the bifurcation of the aorta presented a return of the right femoral pulsation in one day, the left femoral in two days, and both popliteal and dorsalis pedis artery pulsations in eight days. At post mortem, 44 days later, the aortic bifurcation was found totally occluded by thrombus.* One case of embolism to the lower part of the femoral showed a return of pulsation in the inguinal region in two days. In one case of popliteal thrombosis, the femoral pulsation returned in four days. In one case of anterior tibial thrombosis, the posterior tibial pulsation was felt 93 days after the accident. In another anterior tibial thrombosis the popliteal pulsation was felt in 24 hours, and the posterior tibial in 48 hours. In a third case of anterior tibial thrombosis, the posterior tibial pulsation returned in 38 hours.

From the foregoing facts one may assume that if any pulsation will return, it will usually return within four days, and rarely later.

CAUSES OF DEATH

There were 15 known dead patients, eight in the embolic and seven in the thrombotic group. All eight embolic cases died of cardiac failure. Four of the thrombotic group died of cardiac failure; one of cerebral embolism; one of cerebral thrombosis; and one died at home of undetermined cause. All the deaths were, therefore, not due to the peripheral vascular condition of the extremity, but rather to the underlying disease.

SUMMARY

Twenty-nine cases of major and two of minor arterial occlusions are presented. Criteria are given for the differentiation of embolism from thrombosis. The embolic cases were younger in age. Sex was not shown

* Personal communication with Dr. Alfred Angrist, Pathologist of the Jewish Memorial Hospital.

to be a factor in the causation of occlusion. Diabetes was an associated condition in females more often than in males. Fibrillation was a frequent precursor of embolization, but not of thrombosis. Heart disease was the underlying condition in 100 per cent of the cases of embolism and 78 per cent of the cases of thrombosis. There was no specificity of vessel involvement, either in embolism or thrombosis.

The symptoms and signs of sudden occlusions are described.

Acute closures below the popliteal artery seldom caused gangrene. Therapy involving watchful waiting in eight out of 31 cases, gave a loss of limb in 62.5 per cent and a known mortality of 62.5 per cent. Conservative therapy in 23 cases gave a saving of limb in 95 per cent. The hospital stay of conservatively treated cases was 20.8 days less, on the average, than that of the untreated group.

CONCLUSION

The use of alternate suction pressure therapy combined with vasodilating procedures is an efficient method for the treatment of acute peripheral arterial thrombosis and embolism. The adoption of these measures of treatment produces a high percentage of saving of limbs, a low percentage of gangrene, and a lowering of the mortality rate.

I wish to express my appreciation to Dr. A. Goldman, Dr. E. Koffler, Dr. H. Schumer, and Dr. S. P. Sobel of the medical staff for their coöperation in the study of the above cases.

REFERENCES

1. SALAND, G., KLEIN, C., and ZURROW, H.: The thermal reflex vasodilatation test in peripheral vascular disease, *Am. Heart Jr.*, 1939, xvii, 581-584.
2. HERRMANN, L. G., and REID, M. R.: The pavaex (passive vascular exercise) treatment of obliterative arterial diseases of the extremities, *Jr. Med.*, 1933, xiv, 524.
3. LANDIS, E. M., and GIBBON, J. H., JR.: The effects of alternate suction and pressure on blood flow to the lower extremities, *Jr. Clin. Invest.*, 1933, xii, 925.
4. LINTON, R. R.: Acute peripheral arterial occlusion and its treatment, *New Eng. Jr. Med.*, 1937, ccxvi, 871.
5. LUND, C. C.: The treatment of embolism of the greater arteries, *Ann. Surg.*, 1937, cvi, 5.
6. COOK, E. N., and BROWN, G. E.: The vasodilating effects of ethyl alcohol on the peripheral arteries, *Proc. Staff Meet. Mayo Clin.*, 1932, vii, 31.
7. DE TAKATS, G.: The use of papaverine in acute arterial occlusions, *Jr. Am. Med. Assoc.*, 1936, cvi, 1003.

THE TREATMENT OF BARBITURATE INTOXICATION WITH SPECIAL REFERENCE TO Picrotoxin; A REPORT OF 20 CASES *

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THE clinical use of picrotoxin in combating acute barbiturate intoxication is sufficiently new that an experience with 20 cases of this type, observed during the last year and a half, may prove of value. In recent years, the taking of large quantities of barbiturates of various kinds has become an increasingly popular method of attempting suicide. In all of the cases to be described, the barbiturate was taken with suicidal intent, and the patients were seen and treated on the medical services of St. Vincent's Charity and Glenville Hospitals, in Cleveland.

Although Browne¹ discovered, in 1875, that picrotoxin protected rabbits against five to eight times the minimal lethal dose of chloral hydrate, the present clinical use of picrotoxin was stimulated, in 1931, by the experimental work on barbiturate poisoning by Maloney and his associates^{2, 3} at the University of Wisconsin. Since then, the clinical use of picrotoxin in barbiturate poisoning has been reported by Arnett,⁴ Koppanyi, Linegar and Dille,⁵ Kline, Bigg and Whitney,⁶ Gower and Van de Erve,⁷ Bleckwenn and Masten,⁸ Rovenstine,⁹ Lovibond and Steel,¹⁰ Anderson¹¹ and others. Lovibond and Steel, in 1939, reported that 24 cases had been described in the literature, and that in 17 instances, the patient had recovered as the result of treatment with picrotoxin.

CASE REPORTS

In six instances in the series of 20 cases of barbiturate poisoning, picrotoxin was not used, because the intoxication was mild and responded to other methods of treatment.

Case 1. A young woman, aged 20 years, was seen at Charity Hospital three hours after she had ingested 12 amytal tablets. She was in a semi-comatose state, but could be roused by painful stimuli. Her temperature was 97° F.; the pulse rate, 74; the blood pressure, 110 systolic, 74 diastolic; the respiratory rate was 16 per minute. Gastric lavage was carried out immediately and one ounce of magnesium sulphate was left in the stomach. A total dose of four c.c. of coramine also was administered. She recovered promptly, and was discharged from the hospital the day after admission.

Case 2. A Jewish girl, aged 19 years, was admitted to Charity Hospital about 24 hours after she had taken nine tablets of barbital. She was stuporous and semi-comatose and her speech was incoherent, although all reflexes were intact. She had been under treatment for an hysterical neurosis for some time before this incident. She recovered from the toxic effects of the barbiturate without special treatment of any kind.

* Read at the Cleveland meeting of the American College of Physicians, April 3, 1940.

Case 3. A young woman, aged 20 years, took "three pink and four white sleeping powders," and was admitted to Glenville Hospital a few hours afterward. On admission, she was lethargic and her speech was incoherent. The blood pressure was 100 systolic, 80 diastolic; the pulse rate was 120; and the respirations, 10 per minute. Pupillary reflexes were present. Gastric lavage was done, and caffeine and sodium benzoate were administered. No other treatment was necessary.

Case 4. A married woman, aged 41 years, was admitted to Glenville Hospital about 12 hours after she had ingested 25 one and one-half grain phenobarbital tablets. The patient was an obese woman, who was comatose, and displayed no reactions to external stimuli. Her temperature was 99° F.; the pulse rate, 80; and the respirations, 18 per minute. All tendon reflexes were absent, but the pupils were of normal size, and reacted to light. The lungs were clear and the heart normal.

A solution of sodium chloride and glucose was administered intravenously. The patient also received caffeine and sodium benzoate, and 1 c.c. of coramine. No other measures were necessary to arouse her from coma.

The next two cases are of interest, in that the ingestion of the barbiturate was accompanied by large quantities of alcohol.

Case 5. A married woman, aged 38 years, decided to commit suicide because her husband had left her. She drank as much liquor as she could stand, and then tried to find some bichloride of mercury. Failing that, she took seven nembutal capsules. She was admitted to Charity Hospital a few hours later in an excited, talkative and boisterous condition. Physical examination revealed nothing abnormal, except diminished tendon reflexes. The pupils were normal in size, and reacted to light. The patient refused to take anything by mouth, and chloral hydrate was administered by rectum. It is interesting that, in the presence of the alcoholic intoxication, the seven capsules of nembutal did not even induce sleep.

Case 6. A single man, aged 35, had been drinking heavily and taking white sedative tablets. About two hours before he was admitted to Glenville Hospital, he took 20 or more of the tablets. When he was examined, he was unconscious, and appeared cyanotic. He was breathing stertorously, but his pulse was regular, and of good volume. The pupils were of normal size. He could not be roused by painful stimuli, but gastric lavage caused him to thrash about. A 10 per cent glucose solution (500 c.c.) was administered intravenously, and two doses of apomorphine, 1/30 grain each, were given. In addition, oxygen was administered intranasally. After partial recovery, sedatives had to be employed to quiet the patient. He recovered without incident, and was dismissed from the hospital in six days.

In the following case, no picrotoxin was used, because it was not available at the time. This case was one of the earliest in the series, and indicates that other stimulants, such as caffeine and sodium benzoate and coramine are ineffective in combating severe barbiturate intoxication.

Case 7. A single woman, aged 22 years, was admitted to Charity Hospital several hours after ingestion of an unknown quantity of barbital. She was emaciated, comatose and cyanotic, and had gurgling respirations. The pulse rate was elevated to 160 with regular rhythm. The blood pressure was 190 systolic, 80 diastolic. The pupils were contracted and reacted sluggishly to light. The throat was filled with a frothy fluid. The chest was resonant, but the sounds were obscured by bubbling rhonchi. The corneal reflex was present, although all tendon reflexes were absent. Treatment consisted of gastric lavage, suction of mucus from the throat, and the administration of caffeine sodium benzoate, coramine and atropine. No picrotoxin was used. The patient lived 36 hours after admission to the hospital. Before death,

the temperature rose to 105° F., and the pulse rate was 160. The respiratory rate was 50 per minute.

In the next two cases, which also resulted in death, some picrotoxin was used, but in insufficient dosage. Hence these cases should not be regarded as failures of picrotoxin therapy.

Case 8. A married woman, aged 21 years, was admitted to Charity Hospital in a comatose condition. No history was obtainable, but it is probable that she had taken phenobarbital, although the quantity and the time of ingestion could not be ascertained. When she was examined, there was no cyanosis, dyspnea, or acute distress. The temperature was 98° F.; the pulse rate, 96; and the blood pressure, 110 systolic, 50 diastolic. The lungs were entirely clear. The patient was not considered to be in serious condition, and coramine, caffeine, strychnine and sodium chloride solutions were administered. The following day, however, she was still in coma, and the temperature was elevated to 104° F., with a pulse rate of 150. The blood pressure had fallen to 90 systolic, 30 diastolic. The administration of picrotoxin was then instituted, in doses of 6 mg. and 3 mg., at hourly intervals. The patient failed to rally, however, and died the following morning. It is probable in this case that the dosage of picrotoxin was not sufficient, and that too long a time was allowed to elapse before its administration.

Case 9. A single woman, aged 21 years, was admitted to Glenville Hospital early in the morning after she had taken 91 one and one-half grain phenobarbital tablets before retiring the night before. She was comatose, but not cyanotic, and had shallow respirations. All reflexes were absent, and the pupils were greatly contracted. The lungs were clear, and the heart appeared normal.

Concentrated glucose solution was given immediately, and then a 5 per cent solution of sodium chloride and glucose was given continuously by vein. One dose of picrotoxin, 9 mg., was given, but no more was available at the time. Twelve hours after admission, an extensive urticaria developed, and adrenalin was used in an effort to relieve this. Atropine, coramine and caffeine also were administered, but the patient sank rapidly, and died the following morning, 22 hours after admission. The patient had had a psychoneurosis for some time, and her mother also was mentally ill.

In the next two cases, metrazol was used experimentally, as a substitute for picrotoxin. In the first of these, no other treatment was necessary. In the second case, picrotoxin had to be resorted to, but the patient's condition was complicated by pneumonia and she did not recover.

Case 10. A single woman, aged 24, was brought into Charity Hospital three hours after she had taken 18 seconal tablets. The patient displayed no cyanosis, and the pupils were dilated but reacted to light. The pulse rate was 96; the respirations, 12; and the blood pressure 120 systolic, 80 diastolic. Gastric lavage was carried out immediately, and respirations ceased as the tube was withdrawn. Coramine (2 c.c.) was given immediately and artificial respiration was instituted, until breathing was re-established. During the next four hours, the patient received 25 c.c. of metrazol, which brought her out of coma, and she made an uneventful recovery.

Case 11. A married woman, aged 39 years, was admitted to Glenville Hospital about 16 hours after she had ingested 75 one and one-half grain phenobarbital tablets. She was comatose and cyanotic, and her throat was filled with mucus. All tendon reflexes were absent; the pupils were greatly contracted, but exhibited a slight reaction to light, and the corneal reflexes also could be elicited. Numerous bubbling râles were heard in both lungs; these made the heart sounds inaudible. There was tenderness in the lower abdomen, pressure over this area eliciting grunting. The patient's tem-

perature was 101° F.; the pulse rate, 120; respirations, 28; and the blood pressure 90 systolic, 60 diastolic. A little later, the blood pressure had dropped to 60 systolic, 30 diastolic.

During the first 24 hours, the patient was treated with metrazol (12 c.c.). She had a clonic spasm after one dose of 3 c.c. She also received five doses of atropine, 1/150 grain, and two injections of concentrated glucose solution. At the end of this period, the temperature had risen to 105°; the pulse rate was approximately 160; the respirations, 52; and the blood pressure ranged between 100 and 60 systolic, and 50 to 30 diastolic. The patient was in deep coma, and displayed no reactions of any sort.

The second day, sulfapyridine therapy was instituted, and 60 mg. of picrotoxin were given, within a period of 20 minutes. The patient then responded to painful stimuli, and the corneal reflexes could be elicited. She aroused sufficiently to vomit some coffee-grounds material. Her temperature was still 105.2°. Infusions of sodium chloride and glucose solution were administered and an additional quantity of 90 mg. of picrotoxin was given in a period of 20 hours, but the patient failed to rally, and died at the end of this time.

In addition to the preceding case, the barbiturate intoxication was complicated by pneumonia in five other cases. In four of these, giant bullous lesions, ranging in size from 2.5 to 10 cm. in diameter, developed on the skin in areas subjected to pressure.

Case 12. After losing his W.P.A. job, about four o'clock one afternoon, a married, white man, aged 26 years, took 40 grains of amytal. He was admitted to Charity Hospital about five hours later in a comatose condition. His blood pressure was 120 systolic, 60 diastolic; the temperature, 104°; the pulse rate, 100; and the respirations, 24 per minute. All reflexes were absent, and there was urinary and rectal incontinence. The lungs displayed no dullness, but there was much mucus in the throat, which caused bubbling respirations.

Gastric lavage was carried out five or six times, and the administration of picrotoxin was started about an hour after admission. The corneal reflexes could be elicited an hour later, but these disappeared again during the night, although the administration of picrotoxin was continued. The temperature remained elevated, and the respiratory rate increased to 38 a minute. The following morning, the patient was still in deep coma, and the corneal reflexes were still absent. These returned about 20 hours after treatment was begun. A 5 per cent solution of glucose was given intravenously, the picrotoxin was continued, and sulfapyridine also was administered. Milk, water, and coffee were introduced through a nasal tube. The patient regained consciousness about 36 hours after admission. He remained sleepy, but could be roused to talk rationally. A roentgenogram disclosed evidence of broncho-pneumonia, and the sulfapyridine was continued for three days. A week later, the patient had entirely recovered, and was discharged from the hospital.

Case 13. A single woman, aged approximately 30 years, was taken off the Detroit-Cleveland boat, unconscious, and was brought to Charity Hospital. In her luggage a 100 tablet bottle of phenobarbital was found, from which about 80 tablets were missing. When she was first examined, the patient was in deep coma. All tendon and ocular reflexes were absent. The pupils were round and equal and did not react to light. Gurgling râles were audible in the lungs, and the respiratory rate was thirty-two. Later this was diminished to fourteen. The pulse rate was 120 and the blood pressure, 85 systolic, 52 diastolic. There was evidence of peripheral stasis, and there were localized erythematous wheals on the hands and arms.

Gastric lavage was carried out, and the administration of picrotoxin was begun immediately. The following day, the patient appeared in critical condition; the tem-

perature had risen to 105.5°, and the blood pressure to 140 systolic, 100 diastolic. On several dependent portions of her body lesions were discovered which appeared to be subcutaneous hematomas. These later broke down, leaving open ulcers. The largest of these lesions was on the sacrum. Large quantities of glucose and sodium chloride solutions were administered, and caffeine sodium benzoate and sodium salicylate were given, in addition to the picrotoxin. At this time there was considerable edema of the entire body and of the tongue, and a mottled discoloration, due to circulatory stasis. The throat was filled with mucus, which could not be removed readily by suction.

The second day after admission, the skin lesions developed on the elbows and heels, but the patient had less mucus in the throat and appeared to be slightly improved. The therapy was continued intravenously, but the congestion in the chest increased, and she died on the fourth day after admission.

Case 14. A married man, aged 37 years, was admitted to Charity Hospital, in coma. No history was obtainable at the time, but the patient later admitted that he had taken 40 veronal tablets. Because of intense muscular rigidity, an injection of 50 per cent glucose solution, with 3¾ grains of amytal, was administered intravenously. Complete relaxation of the muscles followed immediately. The pupils were of regular size, but reacted sluggishly to light. All other reflexes were absent. The throat contained mucus, and there were numerous râles in the chest, which obscured the heart sounds.

Because no history was available at the time of admission, the diagnosis of barbiturate poisoning was not made until about 24 hours afterwards. The administration of picrotoxin was then started, and sulfapyridine was given for the pneumonia. At this time, the patient's temperature was 105°; the pulse rate, 150; respirations, 45; and the blood pressure 140 systolic, 80 diastolic. Coffee, and sodium chloride and glucose solutions were given, in addition to the picrotoxin.

The characteristic skin lesions appeared in the sacral region, and on the shoulders and feet, on the second day after admission. By the fourth day, the patient was gradually emerging from coma. A week after admission, he was still stuporous, but could be roused to talk rationally. He was out of bed on the tenth day, but had a foot drop and a weakness of one hand, which was considered to be caused by a peripheral neuritis, and vitamin B therapy was instituted. He remained in the hospital for about two weeks after this, to receive supportive treatment. When he was dismissed, he was in good condition, except for mental depression and anorexia.

Case 15. A single man, aged 21 years, was at work on June 30, 1939. The following day, his landlady saw him in bed and thought he was sleeping. The next day he was still in bed, unconscious and foaming at the mouth, so a physician was called, and the patient was sent to Charity Hospital. He was undernourished and so comatose, dyspneic and cyanotic as to appear moribund at the time of admission. His temperature was 105.5°; the pulse rate was 180; the respirations, 60 each minute. All reflexes were absent, the pupils were contracted and did not react to light. There was limited expansion of the chest on the left side and coarse, bubbling râles throughout both lungs. The heart rate was extremely rapid and the sounds were indistinct.

At first, the patient's condition was attributed to severe pneumonia, and sulfapyridine and caffeine sodium benzoate were administered. Within 12 hours, and after learning that he probably had taken 150 grains of barbital, picrotoxin was started.

Two days after admission, red areas appeared over the sacrum, on both heels and on the inner surface of the left foot where it had pressed against the right foot. The redness increased on the sacral areas, and dark, blister-like lesions appeared on the feet, which proceeded to ulcerations. The ulcers healed with the formation of keloids which were still present when he was dismissed from the hospital, about six weeks after admission. Abscesses also formed in the gluteal region which had to be drained.

Within a week after admission, the pneumonia had subsided somewhat, the patient's temperature was reduced, he was rational, and able to take fluids by mouth.

Several weeks later, when he was able to be up and about, he complained of pain in his feet and legs. This was considered to be peripheral neuritis, and vitamin B was prescribed. A little later, there was atrophy of the two medial lumbrical muscles and the hypothenar muscles of the right hand, with loss of pain sensation over the entire surface of the little finger and the medial half of the ring finger, with contracture of the ring and little fingers. The patient was examined by a neurologist who made a diagnosis of impairment of multiple motor and sensory peripheral nerves.

This case is instructive in showing that picrotoxin may be effective even in the most extreme degrees of barbiturate intoxication. The patient had been neglected for at least 36 hours after ingestion of the barbiturates and appeared near death from pneumonia at the time treatment was initiated. This patient also had the troublesome skin lesions and peripheral neuritis, probably as the result of malnutrition, aggravated by lack of food intake occasioned by the barbiturate poisoning.

Case 16. A man, aged 30 years, was brought into Charity Hospital about 18 hours after he had ingested 48 grains of nembutal. He was comatose and cyanotic, and all reflexes were absent. The pupils were of pin-point size. The lungs were resonant and displayed a few rhonchi.

Gastric lavage was carried out immediately and therapy with sulfapyridine and picrotoxin was instituted. The following day, several large blebs which appeared to be filled with gelatinous material developed on the ankles and hips. A culture of material from these lesions showed the presence of *Staphylococcus albus*. Within 48 hours, the patient was fully awake and talking intelligently. The Wassermann reaction was four plus, and the patient previously had undergone treatment for syphilis. About 15 years before, he had also fractured his skull in a fight, following which he had had meningitis and had been in a hospital for about seven weeks.

In four cases, the severe drug intoxication was not complicated by pneumonia or skin eruptions. All these patients were treated with picrotoxin, and all recovered.

Case 17. A young woman, aged 20 years, was admitted to Charity Hospital 45 minutes after ingestion of 72 grains of sodium amytal. She was already comatose, and all tendon, corneal and pupillary reflexes were absent. The pupils were of pin-point size. Her temperature was 96.3°; the pulse rate was 92; and the respirations, 14 per minute. Picrotoxin (156 mg. in solution) was administered intravenously within 24 hours. Fifty-four hours after admission, the patient was sitting up in bed, taking nourishment by mouth, and talking intelligently.

Case 18. About an hour before her admission to Glenville Hospital, a young woman, aged 20 years, ingested 48 one and one-half grain sodium amytal tablets. She was unconscious and all reflexes were greatly diminished. The pupils were of pin-point size, but exhibited a slight reaction. The temperature was 96°; the pulse rate, 90; the respirations, 16; and the blood pressure 124 systolic, 82 diastolic. No picrotoxin was available at the time she entered the hospital, so during the first 12 hours she was treated with strychnine, caffeine and sodium benzoate, and sodium chloride and glucose solution intravenously. Twelve hours after admission, the administration of picrotoxin was started, and 162 mg. in solution were used in the next 24 hours. Within two days, the patient was able to sit up in bed, to take nourishment by mouth, and to answer questions intelligently. She made an uneventful recovery, and was dismissed from the hospital a few days later.

Case 19. A woman, single, aged 27 years, was brought into Glenville Hospital about 12 hours after she had taken 60 grains of ipral-calcium. She was comatose, and all tendon reflexes were absent. The corneal reflexes could barely be elicited and the pupils were greatly contracted, although they still reacted to light. The respirations were shallow, but the lungs were clear. The heart was enlarged, and there was mitral stenosis, with regurgitation. A history obtained later disclosed that the patient had known for three years that she had "leakage of the heart."

Gastric lavage was carried out, and the administration of picrotoxin begun immediately. The total quantity administered was 162 mg., 144 mg. in the first 24 hours, and 18 mg. in the second 24 hours. In addition, sodium chloride and glucose solution (6,000 c.c.) was administered during the first 24 hours. The patient was still very lethargic, but talking incoherently 48 hours after admission. Seventy-two hours had elapsed before she could be roused to talk normally.

Case 20. A married woman, aged 45 years, had been depressed and suffering considerably with insomnia, for which she had been taking phenobarbital. One afternoon she took 24 tablets, and was admitted to Glenville Hospital a few hours later in a deeply narcotized state. She was moderately obese and her skin was flushed, but not cyanotic. All reflexes were sluggish, and the corneal and swallowing reflexes were absent. The pupils were contracted, but reacted to light. The lungs were clear, and the respiratory rate was 28 per minute. The pulse rate was 120, and the heart was not enlarged. The blood pressure was 120 systolic, 80 diastolic.

Gastric lavage was carried out, with magnesium sulphate solution, two ounces of which were left in the stomach. Sodium chloride and glucose solution was administered intravenously. The patient also received oxygen intranasally, and five doses of caffeine sodium benzoate, in addition to the picrotoxin, which was started as soon as she entered the hospital. She received a total dosage of 126 mg. in 42 hours, and made a satisfactory recovery. Her depression was thought to be a menopausal psychosis.

DISCUSSION

In reviewing this series of 20 cases of barbiturate poisoning, certain facts emerge quite clearly, and are worthy of comment.

There is a considerable margin of safety in the use of barbiturates. No extreme intoxications occurred with quantities less than 12 times the usual dosage. The length of time from the ingestion of the drug to the beginning of treatment is extremely important. Even large doses may not cause serious consequences if gastric lavage is carried out within a few hours.

Patients who display a severe degree of bulbar paralysis, with hyperpyrexia, tachycardia, and shallow respirations are doomed to die unless some powerful stimulant is employed immediately. Because of the depression of respiratory function, and the resulting atelectasis, the attending physician must be on the alert to detect the first signs of pneumonia. If there is any evidence of pneumonia, sulfapyridine therapy should be instituted at once. Three patients in this group, with extensive pneumonia and severe barbiturate poisoning, recovered.

In severe cases of barbiturate intoxication, ordinary stimulants are ineffective. These include caffeine, strychnine and coramine. The only cases in which they seemed effective were those of mild or slight degrees of poisoning, and these patients might have recovered without any special treat-

ment. Glucose and sodium chloride solutions administered intravenously, and supplemented in some instances by injections of salyrgan have an important place in the treatment of patients with barbiturate intoxication. In the presence of cyanosis, oxygen is helpful. In our experience, this has been administered only by the inhalation method.

Metrazol has been tried in two cases in this series. One patient recovered with no other treatment. In the other case, picrotoxin was substituted, but the patient died.

Picrotoxin is the drug of choice in treating barbiturate intoxication. It is a powerful stimulant, and in our hands there have been no ill effects from its use. To obtain the best results, it should be instituted promptly if the reflexes are abolished, and should be given intravenously at the rate of approximately 1 c.c. or 3 milligrams each minute until the corneal reflexes reappear and the patient responds to painful stimuli. Thereafter it should be repeated at hourly or at least two-hourly intervals in a dosage sufficient to keep the corneal reflexes active. This requires approximately 3 to 6 mg. an hour, depending on the degree of depression. Whenever the patient is allowed to lapse into a severe depression for several hours, his chances of recovery are greatly lessened.

The occurrence of the skin lesions described in several of the cases was at first rather puzzling. I had not had any experience with skin lesions in barbiturate poisoning before I began using picrotoxin, and hence wondered whether they might be due to the latter drug. For that reason, the dosage of picrotoxin was decreased deliberately in one or two cases, until it was ruled out as the cause.

Various allergic manifestations due to barbital have been described in the literature.¹²⁻¹⁶ These consist of a fine erythematous rash which simulates scarlet fever, and urticarial eruptions, with itching. I have also observed two instances of an influenza-like allergy following the use of theominal (theobromine plus luminal). Vesicular eruptions have also been reported, but I am unaware that anyone else has reported the giant bullous lesions observed in these cases. These vary in size from 2.5 to 10 centimeters. The interesting fact is that they occur only at the points of pressure, but some are well developed within 24 hours after admission. Dr. Clyde Cummer and Dr. C. J. LaRocco have made a special study of these skin manifestations, and plan to report them from the dermatologic viewpoint.

The fact that one patient developed severe peripheral neuritis, and that another showed similar, though less severe, symptoms, emphasizes the importance of nutritional deficiency in these cases. When a patient whose diet has been inadequate is deprived of essential foods and vitamins for several days, because of coma resulting from barbiturate intoxication, clinical signs of a serious deficiency may develop.

It must be remembered, of course, that many of these patients are psychoneurotic and that there is little point in preventing their suicide unless the

proper psychiatric and social treatment is furnished afterwards. Some patients, it is true, are normal mentally, but have had such poor living environment that they are driven to destroy themselves. In these cases, investigation by a social worker, followed by encouragement and the kind of help they need, may restore them to a useful place in the community.

SUMMARY

Twenty cases of barbiturate intoxication as the result of attempted suicide, observed during the past 18 months at St. Vincent's Charity and Glenville Hospitals, in Cleveland, are reported, with special reference to the use of picrotoxin in treatment.

Fifteen patients recovered and five died. Three of the five deaths, however, can not fairly be counted as failures of picrotoxin therapy. In one case, no picrotoxin was used, because it was not available at the time, and another patient received only one dose, for the same reason. In the third case, the quantity of picrotoxin used was insufficient because the patient had not appeared to be in serious condition. In the remaining two fatal cases, the treatment was adequate, but unavailing, because of the severity of the intoxication and widespread pneumonia.

Serious poisoning does not result unless approximately 12 times the usual dose of the drug is ingested.

Ordinary stimulants are ineffective, except in mild cases.

Picrotoxin is effective in the treatment of this condition, and no ill effects have been observed following its use. It must be administered in dosages sufficient to keep the patient in a slightly restless condition. To allow the patient to lapse into deep coma for a period of hours greatly lessens the chance for recovery.

Prompt lavage of the stomach, followed by the injection of glucose and sodium chloride solutions, for diuresis, is an important part of the treatment.

In a number of cases in this series, skin lesions resembling giant bullae occurred in pressure areas. So far as is known, lesions of this type have not been reported previously.

REFERENCES

1. BROWNE, J. C.: On the actions of picrotoxine and the antagonism between picrotoxine and chloral hydrate, *Brit. Med. Jr.*, 1875, i, 409-411, 442-444, 506-542.
2. MALONEY, A. H., FITCH, R. H., and TATUM, A. L.: Picrotoxin as antidote in acute poisoning by shorter acting barbiturates, *Jr. Pharm. and Exper. Therap.*, 1931, xli, 465-482.
3. MALONEY, A. H., and TATUM, A. L.: Picrotoxin as antidote in acute poisoning by shorter acting barbiturates, *Jr. Pharm. and Exper. Therap.*, 1932, xliv, 337-352.
4. ARNETT, J. H.: Ephedrine and picrotoxin used successfully in amytal poisoning, *Jr. Am. Med. Assoc.*, 1933, c, 1593.
5. KOPPANYI, T., LINEGAR, C. R., and DILLE, J. M.: Studies on barbiturates. XIX. Analysis of barbiturate-picrotoxin antagonism, *Jr. Pharm. and Exper. Therap.*, 1936, lviii, 199-228.

6. KLINE, E. M., BIGG, E., and WHITNEY, H. A. K.: Picrotoxin in the treatment of barbiturate poisoning: report of a case, *Jr. Am. Med. Assoc.*, 1937, cix, 328-330.
7. GOWER, W. E., and VAN DE ERVE, J.: Recovery from experimental barbital poisoning and various types of fluid administration, *Jr. Pharm. and Exper. Therap.*, 1938, xlviii, 141-147.
8. BLECKWENN, W. J., and MASTEN, M. G.: The antidotal treatment of barbiturate intoxication: report of treatment with picrotoxin in six cases, *Jr. Am. Med. Assoc.*, 1938, cxi, 504-507.
9. ROVENSTINE, E. A.: The antidotal action of picrotoxin in acute intoxication by the barbiturates, *Am. Jr. Med. Sci.*, 1938, cxvii, 46.
10. LOVIBOND, J. L., and STEEL, G. C.: Picrotoxin in the treatment of barbiturate intoxication: with report of a case, *Lancet*, 1939, ccxxxvii, 561.
11. STEPHENS, J. T., and ANDERSON, J. P.: Picrotoxin in the treatment of barbiturate intoxication: with report of a case, *Ohio State Med. Jr.*, 1939, xxxv, 396-398.
12. LANCASTER, A. H.: Luminal dermatitis with case reports, *South. Med. Jr.*, 1932, xxv, 1142.
13. DOUGHERTY, M. S., JR.: Toxic reactions produced by the derivatives of barbituric acid, *South. Med. Jr.*, 1932, xxv, 1145.
14. MARRI, R.: Acute poisoning by barbituric hypnotics, *Policlinico, sez. prat.*, 1939, xlii, 771.
15. NOVY, F. G., JR.: Drug eruptions due to the barbiturates, *California and Western Med.*, 1938, xlviii, 324.
16. COSTE, F., and BOLGERT, M.: Ulcerations due to barbituric acid preparations, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1933, xlix, 779.

CIRCUMSCRIBED AND ISOLATED BRONCHIECTASIS *

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BRONCHIECTASIS is generally thought of as a widespread and diffuse disease involving the greater part of a lobe, or perhaps several lobes. We have been unable to find references to limited or circumscribed dilatations in American literature and know of but two cases which have been reported in foreign publications.² These two cases showed, one a dilatation involving the axillary branch of the right lower lobe and the other a dilated pectoral branch of the right upper bronchus. Both were of a saccular variety. It was not stated whether or not the contralateral side had been injected.

In searching the files of bronchograms on over four hundred patients at the State Tuberculosis Sanatorium, we have encountered a surprisingly large number of cases in which bronchiectasis was limited in extent. After using the most rigid criteria to establish the fact that the bronchiectasis was limited, we have found six cases that seem sufficiently distinctive to report and two others that we consider as borderline for reasons given below.

The basis upon which we excluded 10 cases was either that the contralateral side for some reason had not been injected or that filling seemed inadequate to rule out the possibility that some adjacent branches might be dilated. The reason for our insistence upon injection of a contralateral side is that very frequently when bronchiectasis is present to an advanced degree on one side, there may be a few branches showing a slighter dilatation on the opposite side. Neither roentgen-ray nor physical examination is sufficiently infallible to permit one to say that the other side is normal: the fact is not established without injection.

Naturally it is also necessary that the injection be sufficiently extensive to include all adjacent branches over a considerable portion of the lung, since obstruction is fairly common in the disease. This should also take care of the objection that the injection of oil revealed only a portion of the disease present.

CASE REPORTS

Case 1. Mrs. M. L. K., white female, 31 years of age, had pneumonia in 1934 and has had sinus disease for years. No other respiratory history. Has never raised any blood but ever since the pneumonia has been expectorating about 5 c.c. of mucoid material in the course of 24 hours. Râles were heard in the right base near the anterior axillary line. Ordinary sputum examinations and Pottenger concentrations were negative for tuberculosis. The ordinary roentgen-ray was of little aid. Bronchogram showed a varicose dilatation of two or three branches of the basilaris medius, the location being just proximal to the costo-phrenic angle (figure 1).

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FIG. 1. Mrs. M. L. K. Note dilatation, indicated by arrow, in the direct continuation of the lower lobe bronchus.

Case 2. Miss I. H., white female, 37 years of age. She had pneumonia at the age of eight and "influenza" in 1931 and 1936. Since the last attack she had expectorated slightly but continuously, but had never produced any blood. Râles were heard in the right cardio-phrenic angle. Her sputum here was of a mucoid character with a little pus and ranged from 15 c.c. to complete absence. The roentgen-ray showed a moderate increase in markings in the costo-phrenic angle on the right. Since several sputums and Pottenger concentrations were negative, she was injected with iodized oil. Bronchogram: Saccular dilatation of two or three branches of the basilaris ventralis (figure 2).

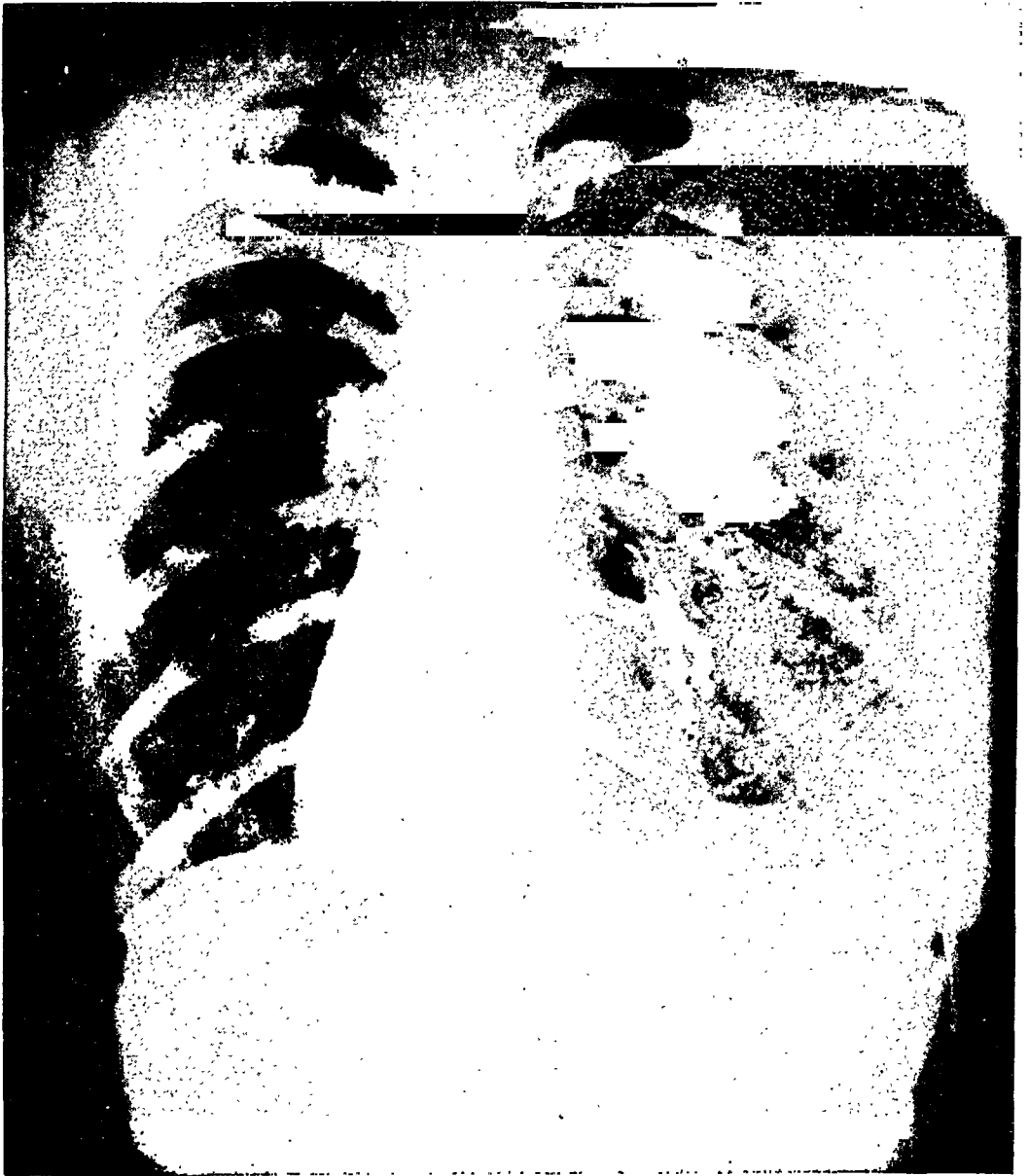


FIG. 2. Miss I. H. Dilatation limited to cardio-phrenic angle.

Case 3. Miss E. S., white female, 17 years of age, had been perfectly well until an attack of "influenza" in 1937. No other respiratory history. Since 1937 she had produced as much as 15 c.c. of sputum fairly regularly each day and on occasions it had been lightly streaked with blood. Râles were heard in the right base. The sputum being negative on ordinary smear and Pottenger concentration, but persisting around 15 c.c. of mucoid material daily, it was decided to inject her, since the routine plate was not significant. Bronchogram: Varicose dilatation of a few branches of the basilaris ventralis in the right cardio-phrenic angle (figure 3).



FIG. 3. Miss E. S. Dilatation limited to cardio-phrenic angle.

Case 4. R. D. H., white male, 26 years of age, claimed that he had been raising about 30 c.c. of sputum daily since two years of age. He had had a recent small hemorrhage. Had "influenza" and pneumonia in 1935, and had had sinus trouble for the past two years. No râles were heard. Repeated sputums were negative on smear and concentration, but since he continued to expectorate about 5 c.c. of muco-pus daily and since his routine plate showed no significant changes, he was injected. Bronchogram: Varicose dilatations of the basilaris medius near the costo-phrenic angle on the right (figure 4).

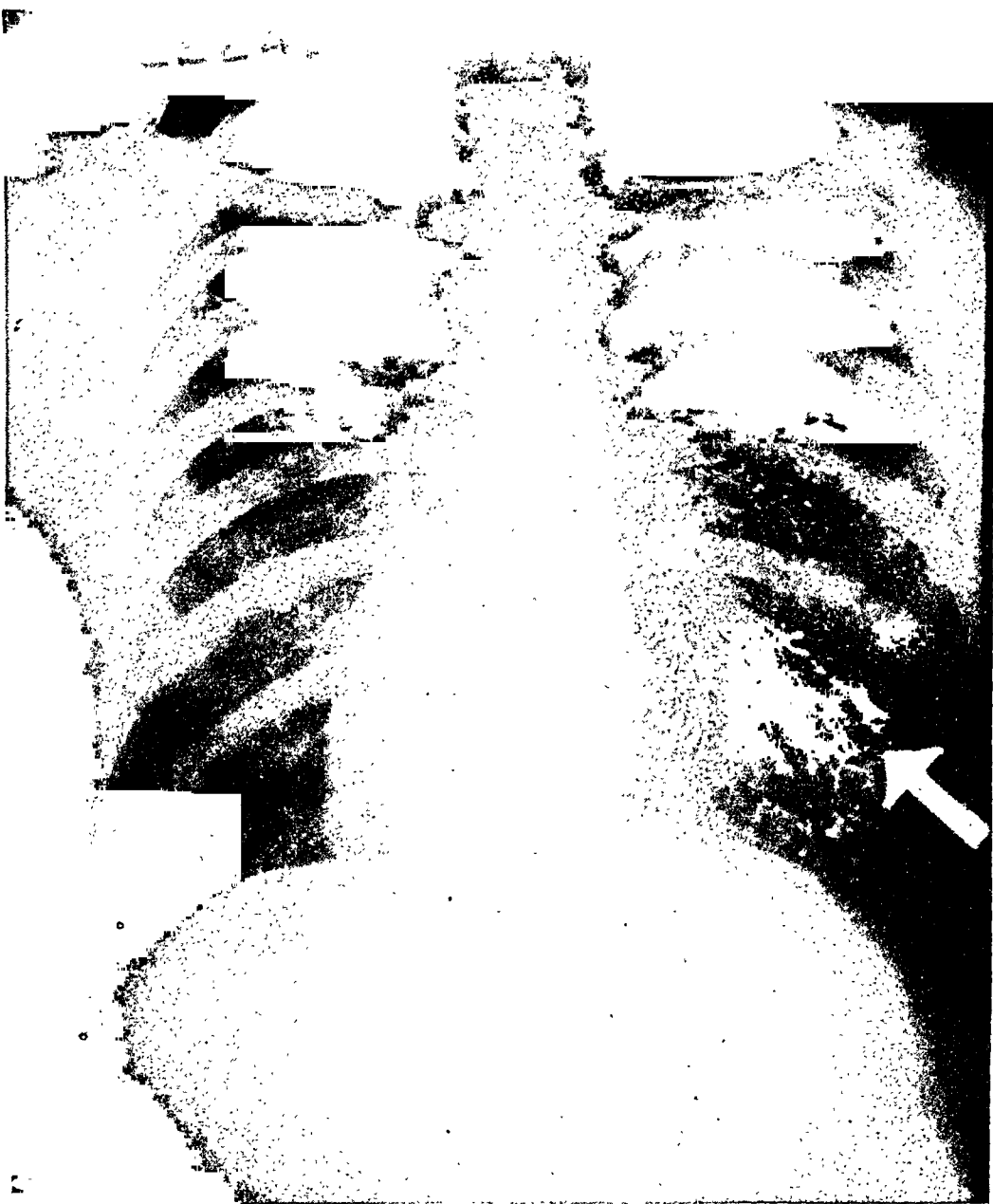


FIG. 4. R. D. H. Varicose dilatations limited to the basilaris medius branches near costo-phrenic angle.

Case 5. Mrs. S. J. R., white female, 30 years of age. Claims to have had "influenza" every winter for 10 years. Had pneumonia at the age of three. Denies expectoration or hemoptysis. Râles were heard in the right base. Sputum was completely absent during her residence in the sanatorium. Roentgen-ray plate showed nothing suggestive. Bronchogram: Cylindrical dilatation and obstruction of the direct continuation of the lower lobe bronchus, terminating in small bud-like dilatations in the costo-phrenic angle area (figure 5).

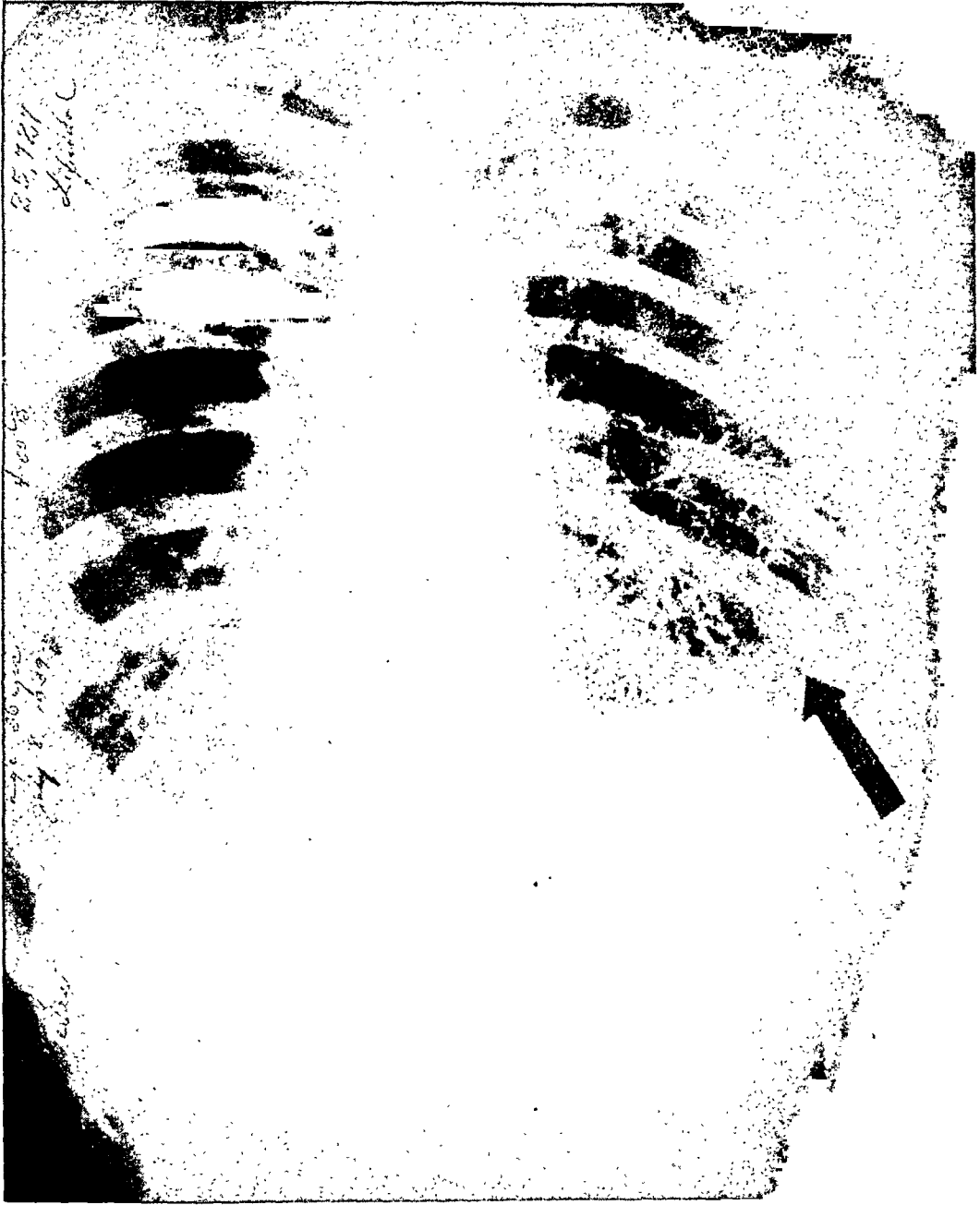


FIG. 5. Mrs. S. J. R. Dilatation in direct continuation of lower lobe bronchus with small saccules in bronchioles.

Case 6. G. A. S., white male, 29 years of age. He gave absolutely no history except of slight chest pain for the past two years. The examiner reported hearing basal râles bilaterally. Sputum remained around 15 c.c. of mucus in 24 hours and was negative on repeated smear and concentration. The routine plate revealed nothing important. Bronchogram: Cylindrical dilatation of cardio-phrenic branches of the basillaris medius, right (figure 6).

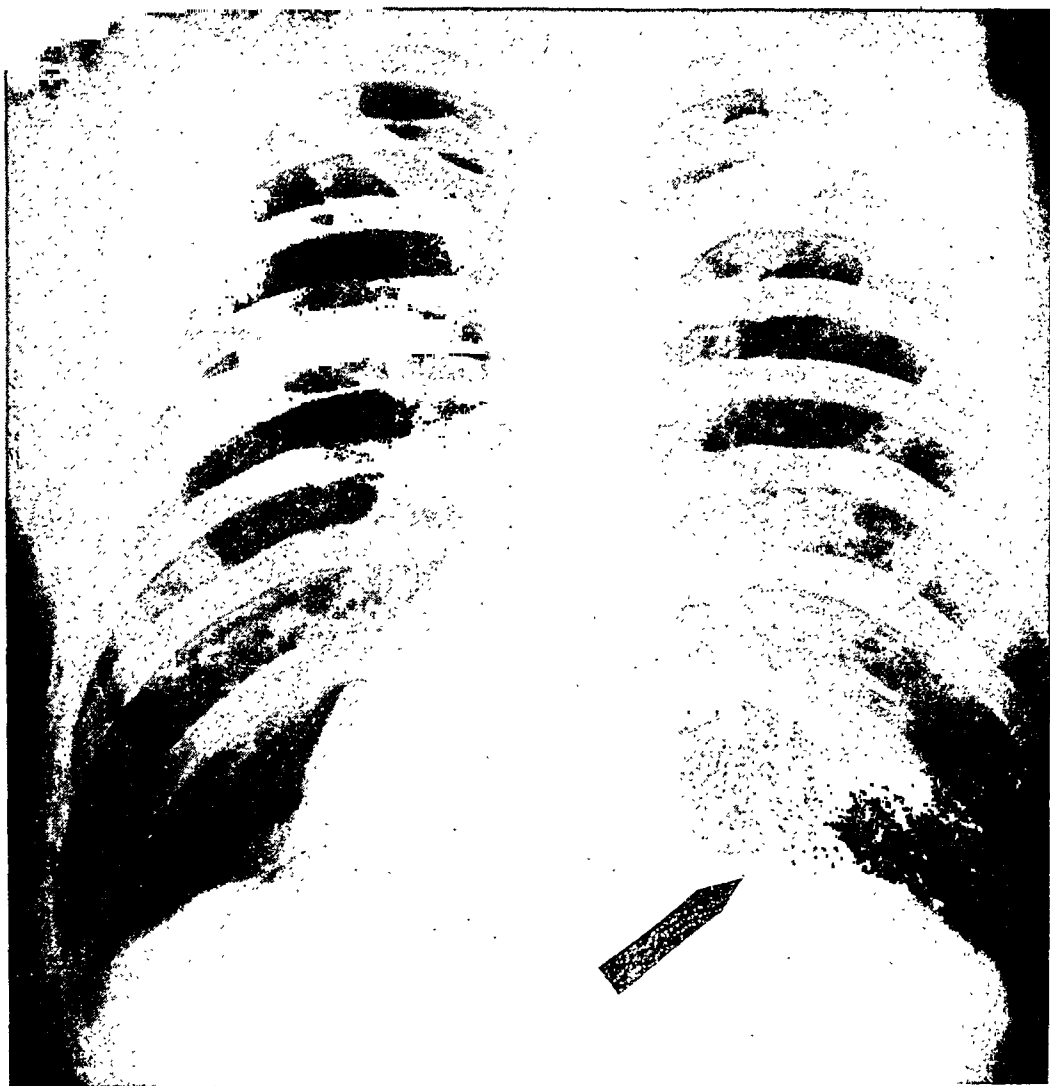


FIG. 6. G. A. S. Dilatations in the cardio-phrenic angle.

Case 7. D. D. W., white male, 54 years of age, had hemorrhage of about 120 c.c. recently and has been expectorating about six months. He had pneumonia in 1917 and 1932 and "influenza" in 1936. In 1928 he had an abscess of the left lung which was treated medically by postural drainage and from which he apparently made a good recovery. His sputum here averaged about 30 c.c. of mucoid material daily and was consistently negative for tubercle organisms. The roentgen-ray plate showed a few strands radiating out into the left periphery about half-way up from the diaphragm. Bronchogram: Saccular dilatations of axillary branches of basilaris medius on the left (figure 7).

Case 8. C. D. A., white male, 29 years of age, had pneumonia in 1935. For about two months has been expectorating about 30 c.c. daily. In addition he has had a small hemoptysis of less than 30 c.c. The sputum here was definitely purulent and was consistently negative for acid-fast organisms. The routine plate showed no significant changes. Bronchogram: A single fusiform dilatation of a bronchiole just above the diaphragm (figures 8 and 9).



FIG. 7. D. D. W. Note sacculations in mid-lung field on left, residuals of an abscess.

As we have commented already, we feel that the last two cases must be regarded with suspicion. Case 7 is obviously an abscess residual and it is impossible to say whether the change represents a parenchymal pocket relined with bronchial epithelium (as we think likely) or a bronchial dilatation. Case 8 is presented largely for the fact that it apparently represents the most limited stage of disease, if we can call it disease. Certainly dilatation is

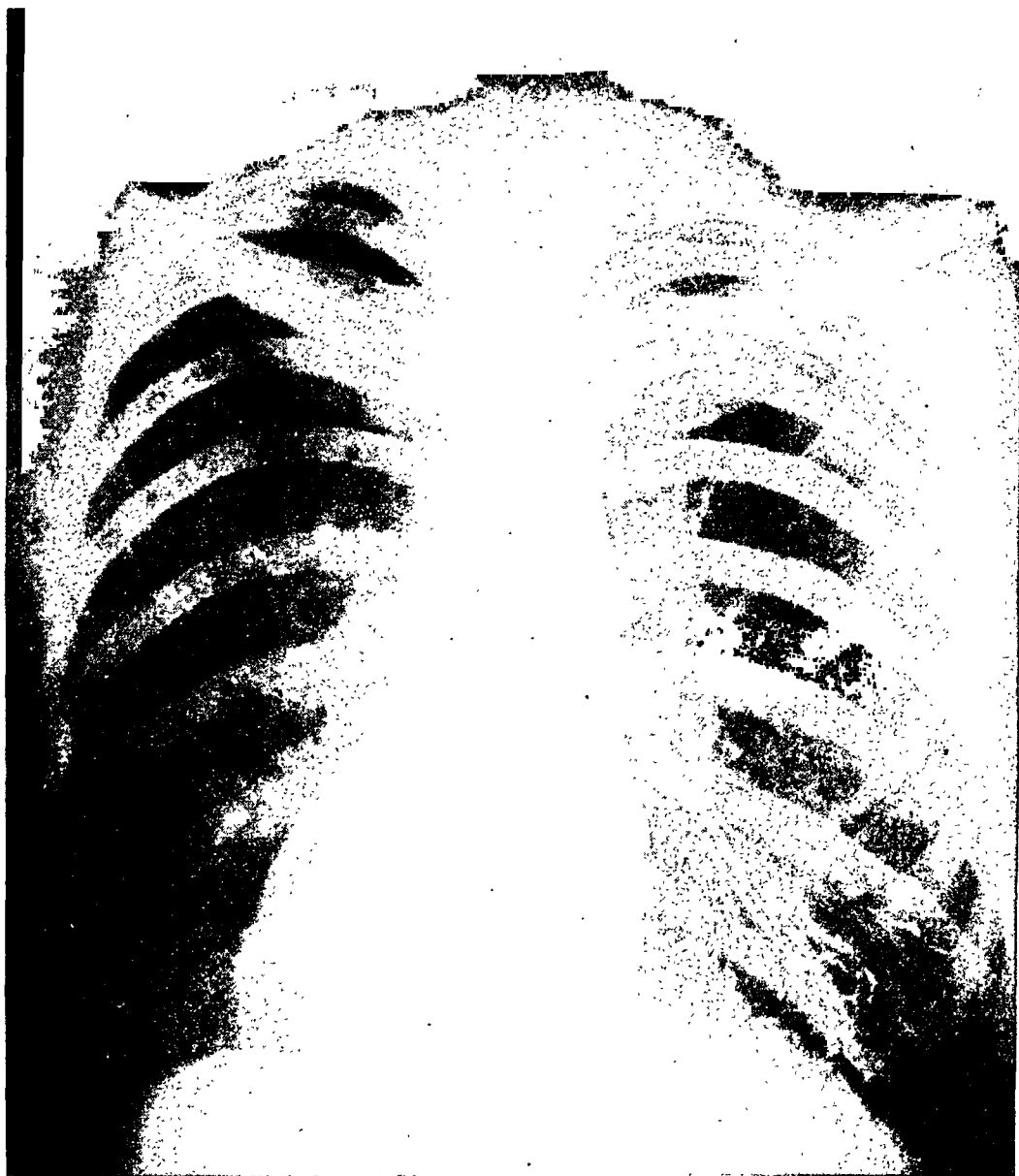


FIG. 8. C. D. A. A single dilatation just above the diaphragm.

present, but in spite of other reports having been negative we did not feel justified in giving the patient a diagnosis of non-tuberculous disease. Certainly we are unwilling to believe that so little dilatation was capable of causing his symptoms. We have seen in our files, however, two other cases in which a single bronchiole was definitely dilated. What their meaning may be we have not been able to determine.

Of the six cases of which we feel convinced, it is apparent that all presented some type of respiratory history, even though slight, and one or two had rather long histories. The sputum in general was but very slightly

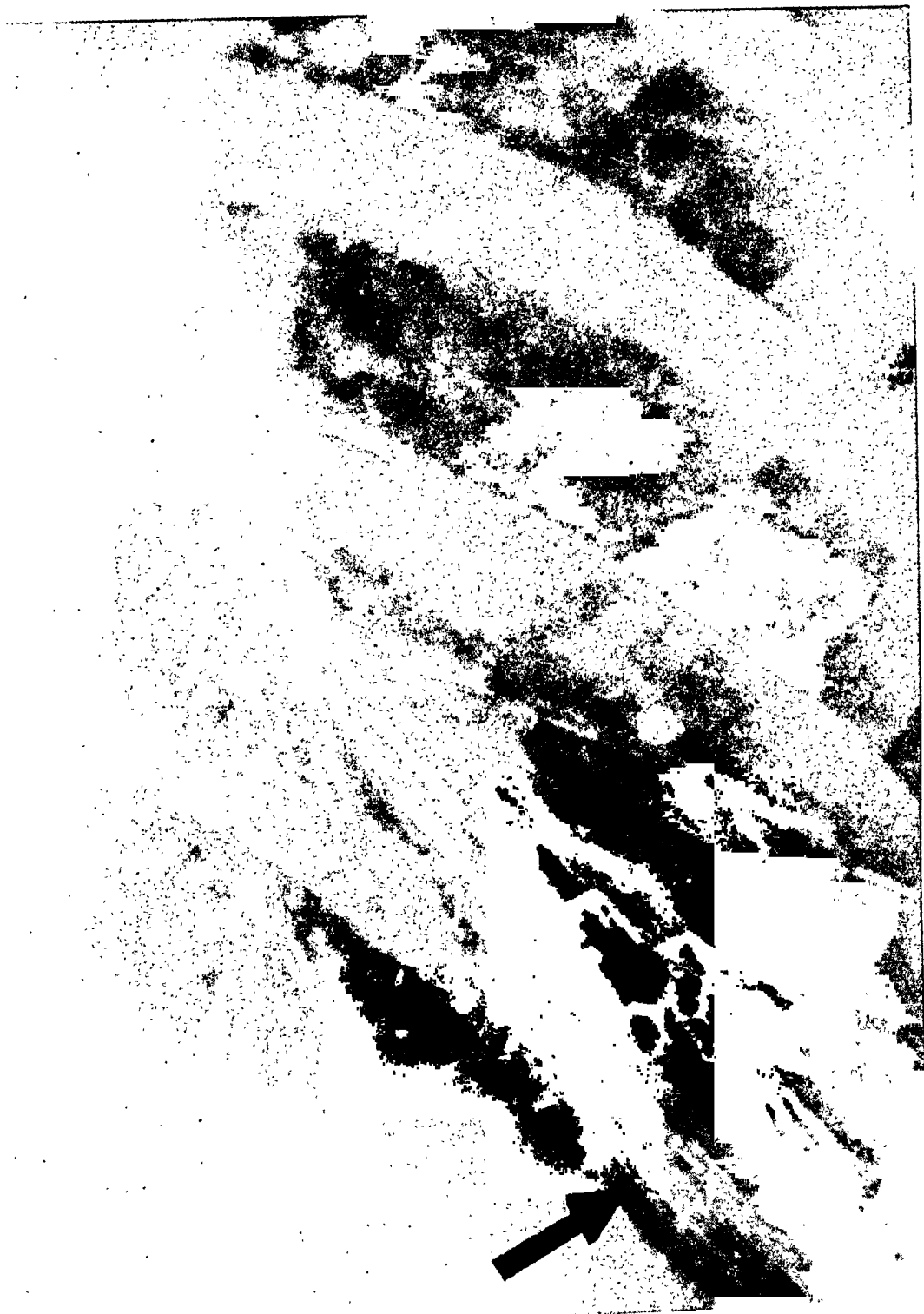


FIG. 9. C. D. A. Enlargement, approximately natural size from figure 8, shows detail of single dilatation. Compare with adjacent branches.

purulent, though one patient produced definite pus in small quantities. Hemorrhage was not prominent and when it occurred was rather slight. On the one hand, then, the symptoms were relatively mild, but on the other they were persistent and consistent.

The question that arises is whether or not there were other dilatations which we failed to find. Short of post mortem there can be no satisfactory answer. We made every effort to rule out such a possibility, but it always exists. We do not believe, however, that it is illogical to think that a few dilatations are capable of producing symptoms of the same type, though not of the same severity, as extensive bronchiectasis. Amberson is of the same opinion.¹ The same pathology that produces severe symptoms in an extensive lesion should be able to produce mild symptoms in a smaller one.

It is perhaps interesting to comment that all the cases which we consider acceptable show dilatations on the right side. Aside from the usual explanation that the right lower lobe has the straightest bronchial connection with the trachea we offer no suggestion as to the reason. Possibly it is nothing more than chance. In view of the fact that the dilatations in previously reported cases were all saccular, we call attention to the variety of types in our cases.

CONCLUSIONS

We present six cases of what we consider to be isolated or circumscribed bronchiectasis which is probably not as rare as the paucity of comment in literature might lead one to believe. It is believed possible that limited dilatation may produce the same quality but not the same degree of symptoms as more extensive disease.

BIBLIOGRAPHY

1. AMBERSON, J. B., JR.: Personal communication.
2. HALL, A. S.: Two examples of localized bronchiectasis, *Tubercle*, 1938, 278.

THE THERAPEUTIC EFFECTIVENESS AND POTENCY OF DIGILANID IN THE TREATMENT OF CONGESTIVE HEART FAILURE*

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OVER a period of years, evidence has been accumulating attesting to limitations of the bio-assay for digitalis bodies. Preparations of the same potency with regard to their ability to produce death in a cat or frog will vary markedly in their therapeutic potency as applied to man. Outstanding examples of this discrepancy are the purified digitalis glycosides, digitoxin, (Merck¹ or "digitaline nativele"²) and Verodigen (Gitalin)^{3, 4} and other members of the digitalis group such as g-strophanthin (Ouabain)⁵ and Urginin.⁶ This marked difference among various digitalis bodies has resulted in confusion. To substitute one preparation for another and still maintain the same level of therapeutic effectiveness requires the clinician to have extensive experience with and knowledge of each drug. It has led to the teaching that the clinician should familiarize himself with a single preparation and avoid the use of any other. Obviously the patient is deprived of the possibility of being treated with a preparation best suited for his individual needs. Furthermore, in our laboratory we have recently found that various samples of digitalis purpurea, although possessing identical cat unit potency, may be weaker or stronger as far as desired clinical therapeutic effects are concerned.

It is because of these limitations and objections to the accepted methods of bio-assay that it is desirable to obtain a digitalis body which can be standardized by gravimetric means. Such a preparation must maintain its potency over long periods of time. What is more important, it should consist of a definite and constant amount of a glycoside or proportion of glycosides which will always produce the same therapeutic effect in a given patient regardless of the sample dispensed.

Recently several digitalis bodies possessing the above qualifications have been introduced. It appeared desirable to study their therapeutic efficacy as compared with the whole leaf of digitalis purpurea. The present report deals with our observations with "Digilanid," † a mixture of constant proportions of three "pure" crystalline glycosides isolated by Stoll and Kreis⁷ from digitalis lanata. None of the three glycosides, known respectively as lanatosides A, B and C singly satisfies the criteria for an ideal digitalis preparation.

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† We are indebted to Sandoz Chemical Works, Inc. for the generous supply of material and other aid in connection with this investigation.

However, when combined with one another in proper proportions,[†] the result is a product of known chemical composition, which, according to the literature⁸ compares favorably with the clinical effects of digitalis purpurea.

SELECTION OF MATERIAL AND METHOD OF STUDY

The study was conducted on bed-ridden and ambulatory patients. Of the former a total of 30 patients was treated orally with digilanid. The final results, however, have been analyzed in only 23 of these, the remainder being excluded either because of insufficient data, administration of other medi-

TABLE I
Characteristics of Ward Patients Used in Study

Patient	Age	Sex	Diagnosis*			Degree† of Congestive Heart Failure	Weight‡ in Pounds
			Etiology	Anatomical	Physiological		
1	38	F	Hypertension	Enlarged heart, dilated aorta	RSR	++	227
2	65	F	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+++	165
3	53	M	Arteriosclerosis	Enlarged heart, myocardial fibrosis, coronary sclerosis	AF	+	147
4	56	M	Hypertension, arteriosclerosis	Enlarged heart, myocardial fibrosis, dilated aorta	RSR	+	164
5	63	F	Rheumatic fever, hypertension	Enlarged heart, mitral insufficiency, mitral stenosis	AF	++	242
6	69	M	Arteriosclerosis	Enlarged heart, myocardial fibrosis	AF	+	134
7	43	M	Hypertension, syphilis	Enlarged heart, dilated aorta, aortitis, ostial stenosis	RSR	±	149
8	57	F	Hypertension, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	RSR	±	174
9	52	F	Rheumatic fever, hypertension	Enlarged heart, mitral insufficiency, mitral stenosis	AF	+	95
10	33	F	Hypertension	Enlarged heart	RSR	++	125 (ca)
11	63	M	Arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis	Auricular flutter	+	112
12	55	M	Hypertension, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	RSR	++	125

* According to criteria for diagnosis established by New York Heart Association.¹⁰

† Determined by general appearance of patient and clinical response during a preliminary period of control.

‡ Before digitalization.

† According to Sandoz Chemical Works, Inc. lanatosides A, B and C are combined in the approximate ratio of 47:16:37 respectively.

TABLE I—Continued

Patient	Age	Sex	Diagnosis*			Degree of Congestive Heart Failure	Weight† in Pounds
			Etiology	Anatomical	Physiological		
13	64	M	Syphilis, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta, aortic insufficiency	RSR	++	138
14	66	M	Arteriosclerosis, unknown	Enlarged heart, coronary sclerosis, myocardial fibrosis	RSR	±	81
15	30	M	Rheumatic fever (active)	Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency, aortic stenosis	AF	+	128
16	58	M	Arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis	RSR	++	132
17	42	M	Rheumatic fever	Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency, aortic stenosis	RSR	+	149
18	69	M	Arteriosclerosis, hypertension	Enlarged heart, coronary sclerosis, myocardial fibrosis	RSR	+	178
19	60	M	Unknown (arteriosclerosis)	Undiagnosed	AF	N	117
20	62	M	Arteriosclerosis, unknown	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	AF	+	119
21	48	F	Unknown (rheumatic type)	Enlarged heart, mitral stenosis, mitral insufficiency	AF	+	166
22	61	F	Hypertension	Enlarged heart	AF	++	237
23	49	F	Hypertension, arteriosclerosis	Enlarged heart, coronary sclerosis, myocardial fibrosis, dilated aorta	RSR	+	176

cation which would interfere with interpretation of results, or because they did not satisfy the criteria used for selection of patients for study. These criteria have been reported in detail elsewhere,⁹ but the main points are worthy of repetition. The etiological diagnosis of the cardiac condition satisfied the criteria established by the New York Heart Association.¹⁰ Patients with complicating conditions such as recent myocardial infarction, bronchopneumonia, chronic diffuse glomerulonephritis or fever of unknown origin were excluded. During the period of hospitalization, the patient must have exhibited some degree of congestive heart failure, although its presence may have been no longer discernible at the time of digitalization. Thus, patients with paroxysmal arrhythmias, but without congestive heart failure have been excluded. Finally, the patient must have been coöperative and capable of taking medication by mouth. This eliminated patients moribund

or too ill to offer a chance for a fair period of observation. Furthermore, none of the patients had received any digitalis preparation three weeks prior to hospitalization. The characteristics of the patients treated on the wards are summarized in table 1.

Following a preliminary control period in which the maximum effect of absolute bed rest, oxygen (if necessary), sedation, limited fluids and dietary restrictions was ascertained, the patient was digitalized rapidly with digilanid orally by one of two plans. The greatest number of patients (18) received within the first 24 hours approximately 0.1 cat unit per pound of body weight (equivalent to approximately 0.033 mg. of digilanid * (table 2) according to the method of Eggleston.¹ The patient was thereafter given large single daily doses equivalent to one half this amount until minor signs of toxicity were evident. The second plan, consisting of single daily doses of approximately 0.05 cat unit per pound of body weight until toxic effects were apparent, was used in five patients (table 3).

At least one electrocardiogram was taken before digitalization and at frequent intervals thereafter, usually daily, until evidence of toxic effects appeared. All patients were weighed daily, since as has been emphasized on several occasions,^{9, 11} the weight curve is the best guide available at present for following the course of the patient's illness and is of particular help in patients with regular sinus rhythm where the diuresis reflected in the weight loss is indicative of a therapeutic effect. All patients were observed closely for evidences of improvement, changes in blood pressure, ventricular and pulse rates and symptoms and signs of toxicity.

In seven patients it was possible to compare the relative potency of digilanid and digitalis purpurea leaf under nearly identical conditions. All the patients received the digilanid first. After a suitable period, from 15 to 20 days, when the electrocardiogram had returned to normal form, digitalis purpurea leaf in tablets of 1 cat unit strength (equivalent to 0.1 gram) was given according to a dosage plan identical with that of the previously administered digilanid.

The suitability of digilanid for maintenance dosage was studied in a group of 20 ambulatory patients with chronic auricular fibrillation. The same care was used in the selection of patients for this group as in the case of those on the ward. All the patients had been under observation for months or years prior to this study so that their maintenance requirement with digitalis purpurea leaf was fairly well known. Since one of the factors under observation was a change in the cardiac reserve it was essential that the patients included for study be free of congestive heart failure when satisfactorily maintained with digitalis. These patients, therefore, were relatively asymptomatic unless their digitalis was discontinued or decreased. Using the cat unit potency as a guide, digilanid was substituted for digitalis

* Each tablet of "digilanid" contains 1/3 mg. of the mixture of the glycosides, lanatosides A, B and C, and is equivalent to 1 cat unit.

TABLE II
Therapeutic and Toxic Doses by Rapid Digitalization with Digilamid

Patient	Weight ¹ in Pounds	Dose First 24 Hours				Therapeutic Effect	Therapeutic Dose					Toxic Effect	Toxic Dose					Remarks	
		Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound	Mg. per Pound		Days Re- quired	Weight ² in Pounds	Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound		Days Re- quired	Weight ³ in Pounds	Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound		
1	227	24	0.106	7.92	0.035	Diuresis, Loss of 7 pounds	1	220 (ca)	24	0.109	7.92	0.036	1	220 (ca)	24	0.109	7.92	0.036	Therapeutic effect overshadowed by toxicity.
2	165	16	0.097	5.28	0.032	VR slowing, Decreased dyspnea	1	165 (ca)	16	0.097	5.28	0.032	2	165 (ca)	23	0.139	7.59	0.016	Patient expired third day after dig- italization.
6	134	15	0.112	4.95	0.037	VR slowing	1	134	15	0.112	4.95	0.037	4	135	33	0.224	10.89	0.070	
7	149	16	0.107	5.28	0.035								7*	145	51	0.331	16.83	0.115	Therapeutic effect indefinite. Mini- mal failure.
8	174	17	0.097	5.61	0.032								2	174	27	0.156	8.91	0.052	Therapeutic effect indefinite. Mini- mal failure.
9	95	10	0.105	3.30	0.034	VR slowing	1	95	10	0.105	3.30	0.034	3	95	19	0.200	6.27	0.066	
11	112	15	0.134	4.95	0.044	VR slowing, Diuresis	2	112	21	0.187	6.93	0.062	5	106	39	0.397	12.57	0.121	Diuresis occurred concomitant with toxic dose. Loss of 6 pounds.
12	125	14	0.112	4.62	0.037								2	124	20	0.161	6.60	0.053	Therapeutic effect overshadowed by toxicity.

¹ Weight prior to digitalization.

² Weight at time therapeutic effect was evident.

³ Weight at time toxic effect was evident.

* Patient missed one dose on third day of digitalization.

† Excluding patient 15.

TABLE II—Continued

Patient	Weight ¹ in Pounds	Dose First 24 Hours				Therapeutic Effect	Therapeutic Dose					Toxic Effect	Toxic Dose					Remarks		
		Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound	Mg.		Days Re- quired	Weight ² in Pounds	Tab- lets or Cat Units	Cat Units per Pound	Mg.		Mg. per Pound	Days Re- quired	Weight ³ in Pounds	Tab- lets or Cat Units	Cat Units per Pound		Mg.	
13	138	15	0.108	4.95	0.036	Diuresis, Loss of 6 pounds	2	132	22	0.166	7.26	0.55	Anorexia, nausea, vomiting.	4	127	36	0.283	11.88	0.093	Diuresis continued after diglanid was stopped. Weight loss of 14½ pounds in 7 days.
14	81	9	0.111	2.97	0.036								Anorexia, nausea, vomiting.	2	78	13	0.166	4.29	0.051	Therapeutic effect indefinite. Mini- mal failure. Overshadowed by tox- icity.
15	128	14	0.109	4.62	0.036	VR slowing	4	122	32	0.262	10.56	0.086	Diarrhea, marked VR slowing.	22	116	140	1.2	46.20	0.378	6 cat units per day for 21 days before toxicity occurred.
17	149	16	0.107	5.28	0.035	Diuresis, Loss of 5 pounds	2	144	22	0.152	7.26	0.050	Multiple VPC's with coupling.	5	137	40	0.291	13.20	0.096	Total weight loss—13 pounds in 9 days.
18	178	20	0.112	6.60	0.037								Anorexia, nausea, diarrhea, visual disturbance, headache, pro- longed PR inter- val to 0.25 sec.	2	176	24	0.138	7.92	0.045	Therapeutic effect indefinite. Mini- mal failure. Overshadowed by tox- icity.
19	117	13	0.111	4.29	0.036	VR slowing	2	117	19	0.161	6.27	0.053	Marked VR slow- ing.	3	118	25	0.211	8.25	0.069	
20	119	13	0.109	4.29	0.035	VR slowing.	2	162	18	0.111	5.94	0.036	Nausea, vomiting.	7	119	49	0.404	16.17	0.135	
21	166	12	0.072	3.96	0.023	Diuresis, Loss 3 lbs.							Nausea, vomiting.	3	162	23	0.172	9.24	0.057	Therapeutic effect indefinite.
22	237	26	0.109	8.58	0.036	Diuresis, VR slow- ing	1	230 (ca)	26	0.113	8.58	0.037	Anorexia, nausea, vomiting, visual disturbance.	2	230 (ca)	36	0.156	11.88	0.051	
23	170	19	0.107	6.27	0.035	Diuresis, Loss of 5 pounds	2	171	27	0.157	8.91	0.052	Anorexia, nausea, vomiting, diar- rhea, prolonged PR interval to 0.25 sec.	2	171	27	0.157	8.91	0.052	
Average †									20	0.133	6.60	0.044				30.2	0.214	10.03	0.071	

TABLE III
Therapeutic and Toxic Doses by Second Plan of Digitalization

Pa- tient	Weight ¹ in Pounds	Dose First 24 Hours			Therapeutic Effect	Therapeutic Dose					Toxic Effect	Toxic Dose					Remarks			
		Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound		Days Re- quired	Weight ² in Pounds	Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound		Days Re- quired	Weight ³ in Pounds	Tab- lets or Cat Units	Cat Units per Pound	Mg. per Pound				
3	147	7	0.047	2.31	0.015	Diuresis. Loss of 4 pounds. VR slowing.	2	143	14	0.098	4.62	0.032	Nausea, vomiting. Abdominal cramps. Multiple VPC's	3	143	21	0.147	6.93	0.018	Total weight loss, 10 pounds in 5 days. Total weight loss, 14 pounds in 12 days. Patient weighed with difficulty.
4	164	7	0.012	2.31	0.014	Diuresis. Loss of 3 pounds	3	162	21	0.129	6.93	0.012	Nausea, vomiting. Anorexia	5	155	35	0.221	11.55	0.073	
5	242	11	0.019	3.63	0.015	VR slowing. Loss of Diuresis. Loss of 4 pounds	2	242	22	0.090	7.26	0.030	Marked VR slowing. Anorexia. Nausea, vomiting	3	238	33	0.138	10.89	0.015	
10	125 (ca)	6	0.048	1.98	0.015	Diuresis. Loss of 6 pounds	2	125 (ca)	12	0.096	3.96	0.032	Nausea, vomiting	3	125 (ca)	18	0.111	5.94	0.017	
16	132	6	0.015	1.98	0.015		4	126	24	0.190	7.92	0.062	Nausea. Visual dis- turbance. Multiple VPC's with coupling. Prolonged PR inter- val, 0.35 sec.	4	126	24	0.193	7.92	0.062	
Average									18.6	0.121	6.14	0.079			26.2	0.168	5.65	0.055		

¹ Weight prior to digitalization.

² Weight at time therapeutic effect was evident.

³ Weight at time toxic effect was evident.

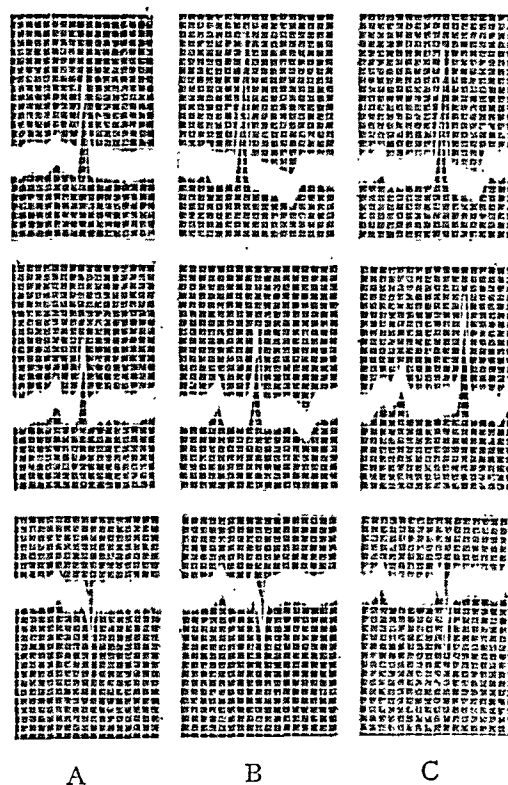


FIG. 1.

FIG. 1. Alterations in electrocardiographic complexes produced by digitalization with digilanid orally.

Patient 1: Hypertensive heart disease with enlarged heart and dilated aorta. (A) control, (B) after 24 cat units (7.92 mg.) in 24 hours, (C) 48 hours after digitalization. Digilanid discontinued after 24 cat units. Patient had marked diuresis with loss of 18 pounds of edema fluid.

leaf in identical doses. At each clinic visit, the patients were observed for alterations in the ventricular rate and development of objective signs of diminution in cardiac reserve. Particular attention was paid to gain in weight (especially if latent edema was suspected), to demonstrable edema of the extremities, moist râles of the lungs and liver enlargement.

RESULTS

The essential data obtained from the use of digilanid in 23 ward patients are summarized in tables 2 and 3. The number of mg. or cat units per pound constituting the therapeutic and the toxic doses of the drug was determined on a basis of the ratio of amount of drug to the weight of the individual at the time the desired effects were discernible. Since patients with edema are continually changing their bodily digitalis concentration as a result of diuresis, it is conceivable that such figures furnish more accurate data than if a single weight be used.

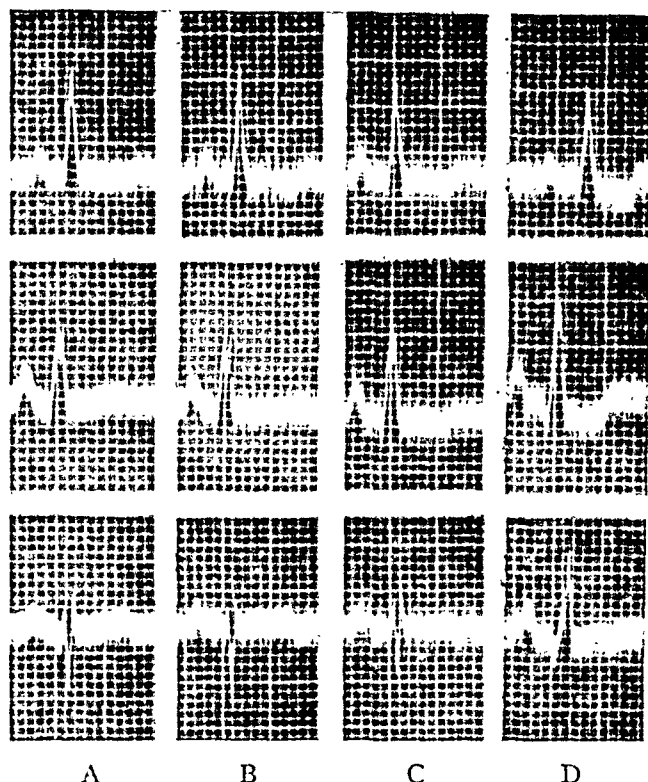


FIG. 2.

Patient 4: Hypertensive and arteriosclerotic heart disease with enlarged heart, myocardial fibrosis and dilated aorta. (A) control, (B) after 7 cat units (2.31 mg.), (C) after 14 cat units (4.62 mg.), (D) after 35 cat units (11.55 mg.). Associated with anorexia, nausea and vomiting.

With the exception of patient 15, a satisfactory therapeutic response was obtained in the group (table 2) digitalized rapidly by the method of Eggleston within one to two days with a dose ranging from 3.30 to 8.91 mg. (average 6.6 mg.) equivalent to 10 to 27 tablets or cat units (average 20 cat units) of digilanid. In six patients the therapeutic effect was indefinite either because of the minimal degree of congestive heart failure or because it was overshadowed by toxic manifestations. In three patients the therapeutic and toxic doses were apparently identical, perhaps due to the rapidity of digitalization. The toxic dose, with the exception of patient 15, ranged between 13 and 51 cat units (average 30.2) equivalent to 4.29 and 16.83 mg. respectively (average 10.03 mg.). Patient 15, a subject with active rheumatic heart disease, required 32 cat units (10.56 mg.) of digilanid over a period of four days before a therapeutic effect could be observed and 140 cat units (46.20 mg.) over a period of 22 days before toxic manifestations occurred.

Of the five patients who were digitalized according to the second plan of study (table 3), it is interesting to note that the therapeutic and toxic doses were within the range of the rapid method and that on the average,

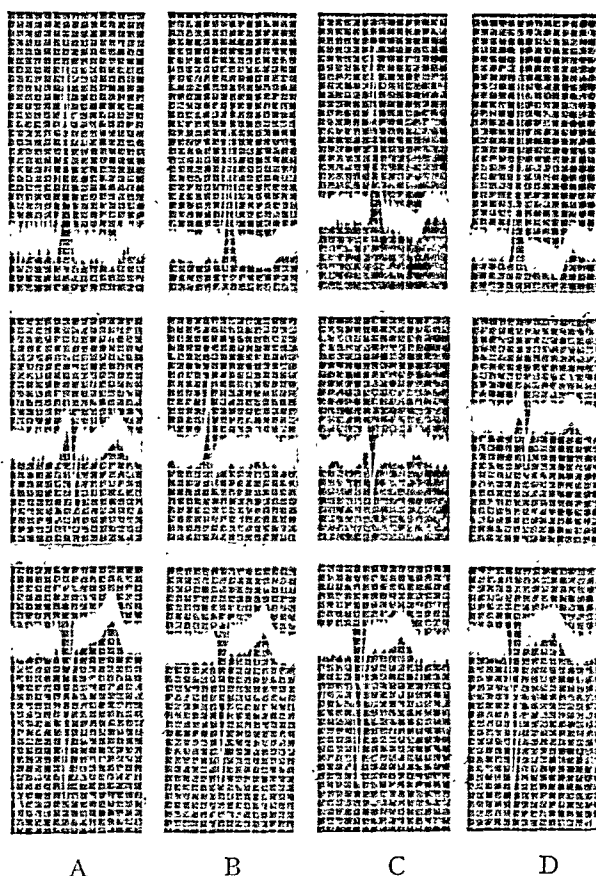


FIG. 3.

Patient 5: Rheumatic and hypertensive heart disease with enlarged heart, mitral stenosis and insufficiency. (A) control, (B) after 11 cat units (3.63 mg.), (C) after 22 cat units (7.26 mg.), (D) after 33 cat units (10.89 mg.). Associated with marked slowing of ventricular rate, anorexia, nausea and vomiting.

18.6 and 26.2 cat units respectively, they were surprisingly lower. Perhaps, if more cases with this method were available for analysis, this discrepancy would not have existed or may even have been reversed.

Comparative studies in seven patients are analyzed in table 4. Considering the impossibility of achieving exactly identical conditions it is striking that four patients (numbers 3, 6, 9, 11) required approximately the same amount of digilanid and digitalis purpurea leaf to produce similar therapeutic and toxic effects. The data on two patients (numbers 10 and 13) would indicate that digilanid was more potent than the leaf, while the opposite is true in the case of patient 4. When the average cat unit values of each preparation required for the therapeutic and toxic effects are compared, the similarity in potency is further emphasized.

Maintenance with digilanid was achieved without difficulty and in the same dose substituted for the digitalis leaf. Patients were observed for varying periods of time amounting in some instances to as long as 7 to 10

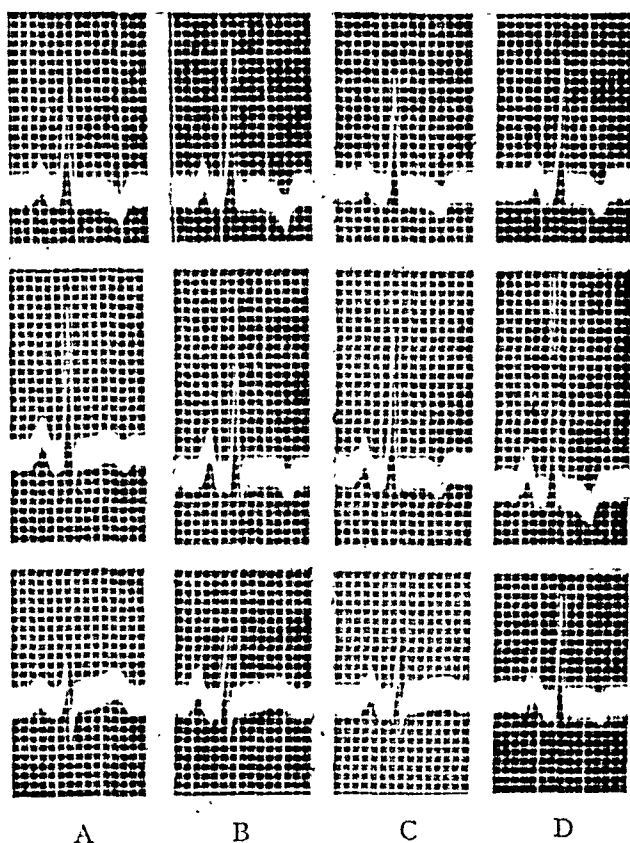


FIG. 4.

Patient 7: Hypertensive and syphilitic heart disease with enlarged heart, aortitis, dilated aorta and ostial stenosis (A) control, (B) after 16 cat units (5.28 mg.), (C) after 23 cat units (7.59 mg.), (D) after 37 cat units.

months. Objective evidence for superiority of one preparation over the other was lacking. An equal number of patients when taking digilanid were subjectively improved or claimed to be worse. However, when subsequent trials were given, the subjective effects were less apparent. In none of the cases were we certain of changes attributable beyond doubt to digilanid.

DISCUSSION

A digitalis preparation to be acceptable for routine clinical use must satisfy many criteria. When administered by mouth, it must be readily absorbable so that in the majority of cases a prescribed dose will produce, within limits of biological variation, a desired effect. The preparation, however, in addition to its ability to be absorbed, must be effective in increasing the cardiac reserve or do any other task required of digitalis. The preparation must be a potent one according to the accepted methods of standardization, although once its potency is thus established, it is desirable to be able to rely for dosage on gravimetric assay. Furthermore its potency must be such that the ratio of toxic to therapeutic dose; i.e., its

TABLE IV
Comparative Therapeutic and Toxic Doses of Patients Digitalized with Digilanid and Digitalis Purpurea Leaf

Patient		Digilanid						Digitalis Purpurea Leaf						Remarks				
		Therapeutic Dose			Toxic Dose			Interval Between Preparations in Days	Therapeutic Dose			Toxic Dose						
Weight ¹ in Pounds	Cat Units	Cat Units per Pound	Days Re-quired	Weight ² in Pounds	Cat Units	Cat Units per Pound	Days Re-quired	Weight ¹ in Pounds	Cat Units	Cat Units per Pound	Days Re-quired	Weight ² in Pounds	Cat Units	Cat Units per Pound	Days Re-quired			
3	143	14	0.098	2	143	21	0.147	3	19	148	14	0.094	2	148	28	0.188	4	Therapeutic effect indefinite for digitalis leaf.
4	162	21	0.129	3	158	35	0.221	5	15	—	—	—	—	160	14	0.087	2	
6	134	15	0.112	1	135	33	0.224	4	20	142	15	0.105	1	142	39	0.274	5	Therapeutic effect indefinite for digitalis leaf.
9	95	10	0.105	1	95	19	0.200	3	19	96	20	0.208	3	92	25	0.271	4	
10	125	12	0.096	2	125	18	0.149	3	16	118	12	0.101	3	116	30	0.238	5	
	(ca)				(ca)													Therapeutic effect indefinite for digitalis leaf.
11	112	21	0.187	2	106	39	0.367	5	18	111	21	0.189	2	109	39	0.357	5	
13	132	22	0.166	2	127	36	0.283	4	19	—	—	—	—	129	64	0.495	8	
Average		16.4	0.128		28.7	28.7	0.227				16.4	0.139			34.1	0.272		

¹ Weight at time therapeutic effect was evident.

² Weight at time toxic effect was evident.

therapeutic range, be large. Cumulation and elimination of the drug must be at a rate compatible with the possibility of producing complete digitalization and subsequently maintaining this level satisfactorily. The preparation must be stable and the potency of various lots should not vary. Finally, it must be easy to administer and tolerated by the patient as far as local gastrointestinal irritation is concerned.

Digilanid is readily absorbable and its effectiveness as far as could be determined appears to be identical with powdered digitalis leaf. A satisfactory therapeutic response is obtained with both the bed-ridden and ambulatory patients. In the former diuresis and slowing of the ventricular rate, if the patient has auricular fibrillation occurred in the majority of patients within a reasonably short period of time. Furthermore, characteristic alterations of the electrocardiogram (figures 1 to 4) are produced with a dose comparable to that of digitalis.

The clinical potency of digilanid, cat unit for cat unit, appears to be identical with that of digitalis purpurea leaf. The average therapeutic dose of 20 cat units and toxic dose of 30 cat units are in close agreement with the generally accepted figures for the leaf. The similarity is further strengthened by the data obtained in the seven patients (see table 4) in whom both preparations were compared and in the ambulatory group where one preparation was substituted for the other. In the latter group, there were no consistent differences found in either the subjective or objective effects. In a few cases questions arose concerning subjective advantages or disadvantages, but in all instances, when tried a second time after an interval, the apparent difference was not repeated.

The ratio of toxic to therapeutic dose also appears to coincide with the general experience in the use of digitalis. Individual variations are to be expected, but with the exception of the three patients who became toxic too rapidly to determine the therapeutic dose and of patient 15, who had active rheumatic heart disease, the therapeutic effects occurred after administration of between 45 per cent and 76 per cent of the toxic dose.

It is not sufficient that a preparation produce digitalization when administered at repeated short intervals, but the rate of elimination and therefore its ability to accumulate must be such that slow digitalization and maintenance of a desired therapeutic effect is possible. Digilanid also satisfies this criterion. This is well illustrated in the group of five patients digitalized by our second plan of study and in the group receiving a maintenance dose within the limits set by clinical experience.

No difficulty was experienced with regard to the administration of the preparation. Although gastrointestinal irritation was to be expected with any drug taken by mouth this was not observed in the 43 patients studied. This in itself may be a minor advantage of digilanid over digitalis leaf, but the number of cases reported is not sufficiently large to warrant this conclusion.

As pointed out in the introduction, one of the disadvantages in the use of digitalis leaf is the varying clinical potency in man although the different samples of leaf possess identical cat unit values. If the gravimetric method of assay permits greater accuracy and uniformity of dosage regardless of the sample dispensed, then digilanid would possess definite advantages over the powdered leaf of digitalis purpurea.

Experience with digilanid, therefore, permits one general conclusion. The mixture of pure crystalline glycosides combined in constant proportions satisfies with a high degree of perfection the criteria for a satisfactory digitalis preparation. The similarity of digilanid and digitalis leaf with regard to fundamental pharmacological and clinical properties is impressive. This is in close agreement with the recent report of Adams and Gregg.¹²

SUMMARY

1. The therapeutic efficacy and potency of digilanid, a mixture of pure crystalline glycosides present in digitalis lanata, has been studied in 23 hospitalized and 20 ambulatory patients.

2. The therapeutic and toxic doses of digilanid in terms of cat unit potency were found to be identical with those of digitalis purpurea.

3. The similarity of digilanid and digitalis leaf with regard to fundamental pharmacological and clinical properties is discussed.

4. Digilanid satisfies the established criteria for a reliable potent digitalis preparation.

BIBLIOGRAPHY

1. EGGLESTON, C.: Digitalis dosage, Arch. Int. Med., 1915, xvi, 1.
2. GOLD, H., KWIT, N. T., and CATTELL, M.: Studies on purified digitalis glucosides. I. Potency and dosage of "digitaline nativele" by oral administration in man, Jr. Pharm. and Exper. Therap., 1940, lxix, 177.
3. STROUD, W. D., LIVINGSTON, A. E., BROWN, A. W., VANDER VEER, J. B., and GRIFFITH, G. C.: Use of Verodigen (a digitalis glucoside) in cardiovascular disease; its biological assay and pharmacological action, ANN. INT. MED., 1934, viii, 710.
4. LEVY, H., and BOAS, E. P.: Clinical studies of gitalin and of digitalis in the treatment of auricular fibrillation, Am. Heart Jr., 1938, xv, 643.
5. WYCKOFF, J., and GOLDRING, W.: Intravenous injection of ouabain in man, Arch. Int. Med., 1927, xxxix, 489.
6. CHAMBERLAIN, F. L., and LEVY, R. L.: Clinical study of a preparation of squill (urginin) in the treatment of myocardial insufficiency, Am. Heart Jr., 1937, xiv, 268.
7. STOLL, A., and KREIS, W.: Ueber genuine Digitalis-glukoside, München. med. Wehnschr., 1933, lxxx, 723.
8. (a) HOCHREIN, M., and LECHLEITNER, H.: Zur Klinik der Digitaliswirkung. Erfahrungen mit dem neuen Digitalispräparat "Digilanid," München. med. Wehnschr., 1933, lxxx, 727.
(b) LUTEMBACHER, R.: Les glucosides de "digitalis lanata"; étude clinique, Presse med., 1933, xli, 1709.
(c) JANSON, P.: Digilanid, ein neues Hertzmittel, Ztschr. f. Kreislaufforsch., 1934, xxvi, 463.

- (d) JANSON, P.: Klinische und ambulante Erfahrungen mit Digilanid, dem neuen Digitalispräparat Sandoz, *Therap. d. Gegenw.*, 1934, lxxv, 45.
- (c) BERTHEAU, H.: Klinische Erfahrungen mit Digilanid, *Deutsche med. Wchnschr.*, 1934, lx, 1504.
- (f) NIETEN, L.: Ueber Digilanid—Therapie bei Herzkranken, *Therap. d. Gegenw.*, 1935, lxxvi, 253.
- (g) BAUKE, E. E.: Klinische Digilanidstudien bei intestinaler und parenteraler Verabreichung, *Deutsche med. Wchnschr.*, 1935, lxi, 371.
- (h) ROTH, O.: Ueber Herztherapie unter specieller Berücksichtigung des Digilanid, *Schweiz. med. Wchnschr.*, 1935, lxxv, 741.
- (i) ROLLER, D.: Die Indikationen und Anwendung von Digilanid, *Therap. d. Gegenw.*, 1937, lxxviii, 162.
- (j) VON SACHS, E.: Klinische Erfahrungen mit Digilanid bei enteraler und parenteraler Zufuhr, *Zentralbl. f. inn. Med.*, 1937, lviii, 849.
- (k) ROHR, K., and WUHRMANN, F.: Vier Jahre klinische Erfahrungen mit Digilanid unter besonderer Berücksichtigung einiger therapeutischen Eigenschaften, *Schweiz. med. Wchnschr.*, 1938, lxxviii, 261.
- (l) JUNET, R., and BIANCHI, M.: Étude clinique d'un nouveau digitalique: le digilanide, *Rev. méd. de la Suisse Rom.*, 1939, lix, 139.
- (m) OETTEL, H.: Digitalis lanata. Klinisch gesehen: Tatsachen und Wertung, *Med. Klin.*, 1939, xxxv, 1628.
- 9. BATTERMAN, R. C., ROSE, O. A., and DEGRAFF, A. C.: The combined use of ouabain and digitalis in the treatment of congestive heart failure, *Am. Heart Jr.*, 1940, xx, 443.
- 10. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, Ed. 4, 1939, New York Heart Association, New York.
- 11. DEGRAFF, A. C., NADLER, J. E., and BATTERMAN, R. C.: A study of the diuretic effect of mercupurin in man, *Am. Jr. Med. Sci.*, 1936, cxc, 526.
- 12. ADAMS, W., and GREGG, L.: Clinical comparison of the crystalline glucosides of digitalis lanata (digilanid) and the powdered leaf of digitalis, *Am. Heart Jr.*, 1940, xix, 576.

THE FOLLICULAR TYPE OF MALIGNANT LYMPHOMA; A SURVEY OF 63 CASES *

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SO-CALLED follicular lymphoma was first identified by Brill, Baeher and Rosenthal in 1925.² They did not at this time consider it a neoplastic phenomenon and suggested the term giant follicle hyperplasia. Shortly afterward several similar cases were recorded by Symmers, who likewise assumed a non-neoplastic background.⁸ The former authors ultimately revised their beliefs and at the present time consider the disease a form of lymphoblastoma.^{1, 7} Symmers, however, has retained his original concept, although admitting frequent transition of the process into frank neoplasm.⁹ Callender included this disease in the group of hematopoietic tumors³ and Jackson has stated that the disorder frequently progresses into one of the other forms of malignant lymphoma.^{5, 6}

The series which we report consists of 63 cases of follicular lymphoma, biopsy or necropsy material from which was submitted to the Laboratory of Pathology of the Massachusetts General Hospital during the period from 1917 to 1939. Fifty-nine had relatively complete clinical data and in 29 there was sufficient roentgenologic material for thorough analysis. Discussion has been divided into histologic, clinical, roentgenographic and therapeutic observations in order to demonstrate the identity of the disease.

PATHOLOGIC OBSERVATIONS

The striking fashion in which the histologic structure of follicular lymphoma differs from that observed in other types of malignant lymphoma probably accounts for the fact that its incorporation into this category is a comparatively recent event. In fact, the apparent resemblance to the structure of simple lymph node hyperplasia has caused several authorities to consider the disease merely a manifestation of chronic non-neoplastic irritation. There can be no question, however, that the condition leads almost invariably to a lethal outcome and the clinical manifestations are so similar to those exhibited by other forms of lymphoma that we have not hesitated to consider it a histologic variant of this disease complex. Jackson⁶ has stated that it represents an early form of malignant lymphoma and may become transformed into any of the other recognized types. Callender has frankly considered it to be a lymph node tumor and attributed to it a rapidly fatal course.

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In our material, follicular lymphoma has been manifested by moderate to enormous enlargement of lymph nodes with replacement of the normal architecture by multiple follicle-like nodules of varied size and approximation. Normal sinus structure was obscured and the capsule frequently encroached upon. Invasion of perinodal tissues was not common but when present, interestingly enough, exhibited follicle-like arrangement even beyond the confines of the lymph node (figure 3).



FIG. 1. Nodal structure intervening between follicles consists of a "matrix" of closely packed lymphoid elements obscuring the normal architecture. The follicles which are Type I in character exhibit the "cracking-off" phenomenon. $\times 150$.

Review of the sections revealed two essentially fundamental structural variations. One consisted of closely packed, rounded or oval shaped, follicle-like nodules of inconstant size but similar intrinsic morphology (figure 2). The intervening tissue consisted only of thin strands of small lymphocytes or compressed reticular substance. The other type also consisted of innumerable widely distributed follicles exactly similar to those noted above. Instead of lying in immediate proximity to each other, however, they were separated by broad homogeneous masses of small lymphocytes (figure 1). The follicles seemed set, more or less, in a lymphocytic matrix which was otherwise characteristic of the so-called lymphocytic form of lymphosarcoma. In these the architecture of the node appeared to be more completely obliterated by the combined processes.

Silver stains for argentophilic fibrils revealed a characteristic revision of supportive structure; this in the reticulum framework of the lymph node. In



FIG. 2. (Left) Follicles are homogeneous in character (Type I). Intervening stroma is compressed, but normal landmarks persist. $\times 75$.

FIG. 3. (Center) An example of extranodal invasion in which follicular arrangement is evident. The two follicles are encompassed by pericapsular fat. $\times 200$.

FIG. 4. (Right) A silver stain demonstrating the reticulum structure of a normal lymph node. $\times 200$.

normal lymph nodes this procedure demonstrated no staining of the collagen fibers composing the capsule and major trabeculae. Extending from these, however, was a loose, fairly regular meshwork of fine argentophilic reticulum fibrils (figure 4). At the edges of the sinuses and follicles the reticulum showed abrupt transition to a relatively sparse, irregular, noninterlacing prolongation of fibrils.

In follicular lymphoma a distinct revision of fibrillar elements appeared. The reticulum meshwork surrounding each nodule was distorted and condensed by follicular expansion (figure 5). The normal loose network with

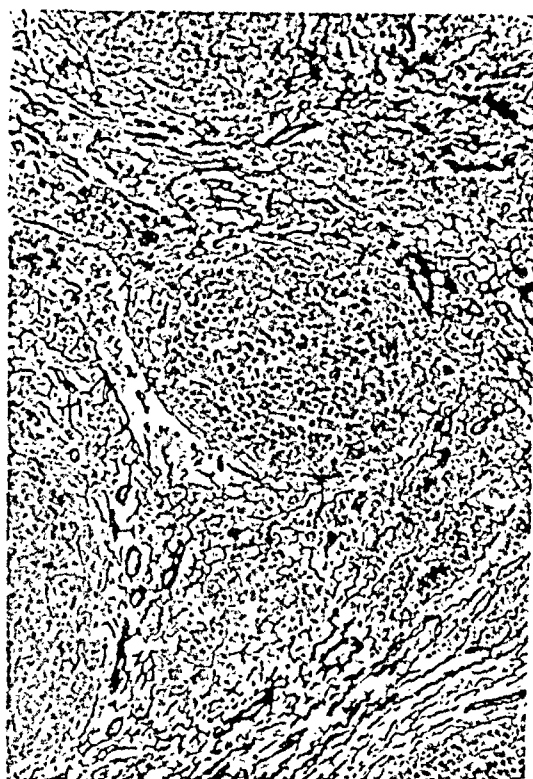


FIG. 5. A silver stain of follicular lymphoma. The compressed character of the reticulum fibrils with absence of collagenization may be observed. $\times 200$.

broad polygonal pulp spaces became compressed and the interreticular crevices were elongated and narrowed. The disappearance of the sinuses appeared to be the result of the displacement of reticular substance and pulp content. Despite the condensation of fibrils, fusion and collagen formation did not occur. All other types of lymphoma produced destruction of reticulum with the reappearance in some of scanty disconnected fibrils and in others of a fibrous stroma with no resemblance at all to the normal architecture. Ordinary hyperplasia caused no significant reticular rearrangement. This feature was, therefore, of considerable morphologic diagnostic value.

The compactness of the reticulum at the periphery of each of the nodules caused the transition into the follicles to become even more abrupt than usual.

Such fibrils as were observed extending into the follicles were few, irregularly arranged, frayed, and stunted in appearance. These sparse, stretched attachments to the surrounding framework were often ruptured in the course of fixation and sectioning, and permitted separation of the follicles from the encompassing stroma. "Cracking off" of nodules was admittedly an artefact but it was sufficiently peculiar to follicular lymphoma and so relatively inconspicuous in nonspecific hyperplasia that it was believed to offer a degree of differential diagnostic assistance (figures 1 and 2).

Sections stained in the routine manner with phloxine and methylene blue after fixation in Zenker's fluid were studied for the purpose of distinguishing

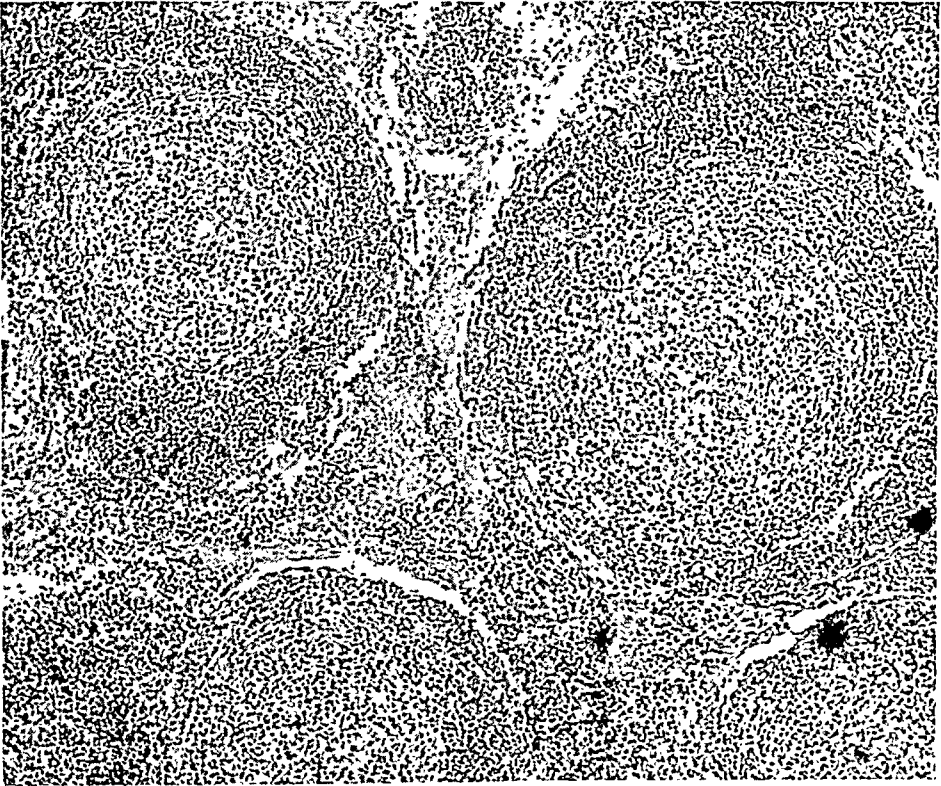


FIG. 6. An illustration of Type II follicles with well defined germinal centers. $\times 200$.

fine cytologic variations. The dual character of the pulp intervening between nodules has been discussed above. Follicular components when subjected to detailed examination were found to exhibit a more marked variation than was originally suspected. Transition forms of all sorts were noted from nodules with relatively simple structure to those which were sufficiently complicated to offer difficulty in recognizing the basic follicular background. Despite a wide degree of morphologic overlapping, however, the follicular nodules were found to be susceptible to division into four major forms, arbitrarily termed Types I to IV.

The simplest of these, Type I consisted of homogeneous nodules comprised uniformly of small lymphocytes without germinal center formation or

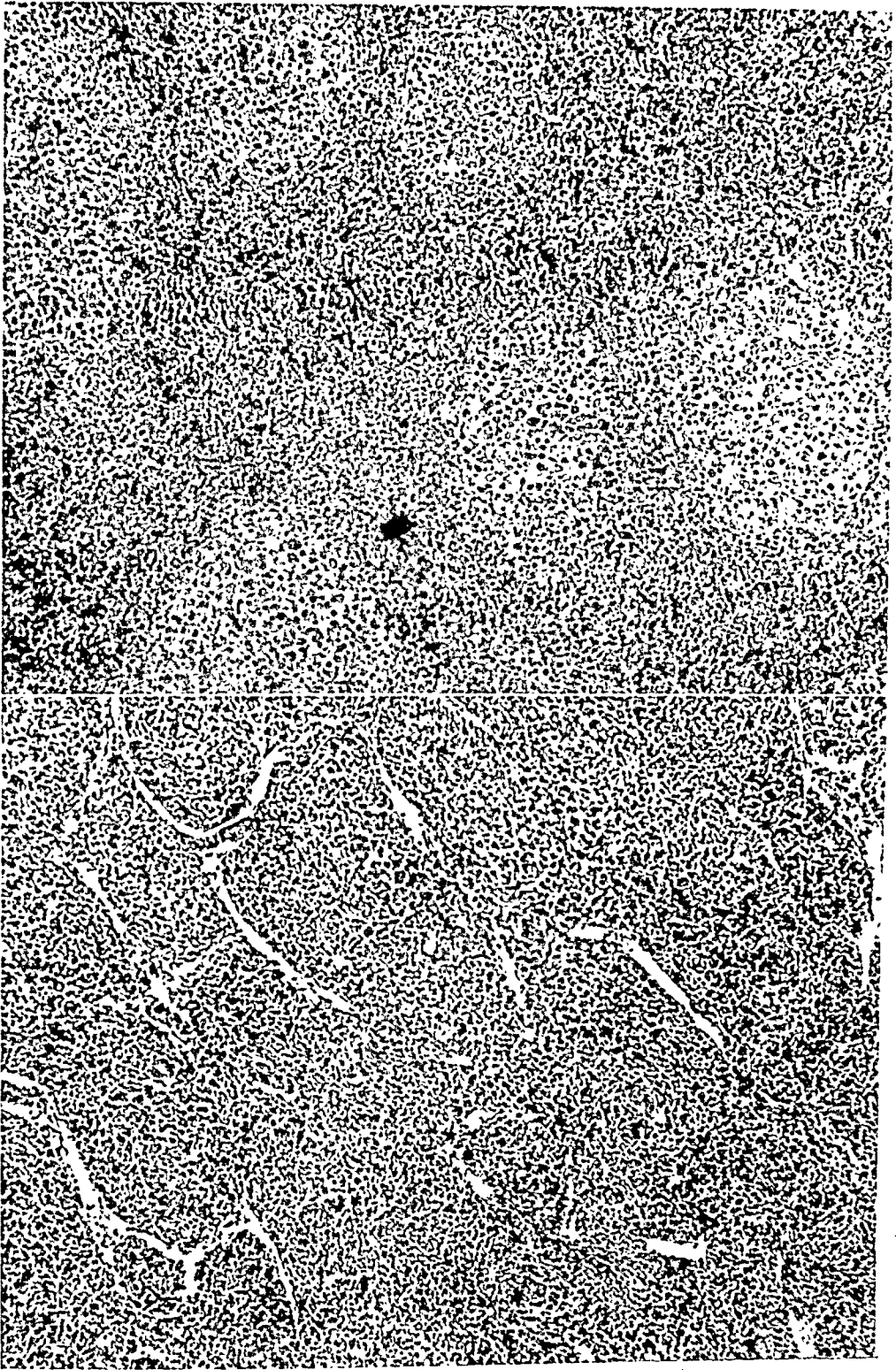


FIG. 7. (Above) Type III follicles with loss of peripheral rims of small lymphocytes. The follicles consist wholly of loosely arranged, polymorphous, germinal center elements. $\times 200$.

FIG. 8. (Below) The interlacing strand-like arrangement of the follicles in the Type IV lesion. There is fusion of many nodules composed wholly of polymorphous elements but the follicular background is still perceptible. $\times 200$.

significant intermixture with less mature elements (figures 1 and 2). Follicles classified as Type II showed slight to marked germinal center formation (figure 6). The central contents of these consisted of pale staining, compactly and occasionally concentrically arranged cells, the nature of which was difficult to determine with unequivocal accuracy. Some appeared to be primitive stem cells with large, round, vesicular nuclei, prominent nucleoli with scanty radially arranged chromatin, and ill defined, inconstantly staining cytoplasm. Other cells, approximately 10 to 15 microns in diameter, possessed a well delimited, abundant eosinophilic cytoplasm, and dark staining, irregular, reniform nuclei. These occasionally exhibited a phagocytic character and were not unlike clasmatocytes in appearance. Mingled with these elements were a few lymphoblast- and lymphocyte-like cells and moderate numbers of mitotic figures. Surrounding the germinal center and varying in thickness inversely with the size of the center, was a rim of wholly mature lymphocytes. The nodules were all uniformly round or oval in shape although there was considerable variation in diameter.

Three essential modifications distinguished the Type III lesion. The follicular rim of lymphocytes was lost and the entire nodule was made up of germinal center elements (figure 7). Among these the phagocyte-like cells predominated but many had assumed bizarre form and anaplastic qualities. Nuclei were larger, somewhat more vesicular, and there were increased numbers of mitotic figures. The cells were not unlike those observed in reticulum cell sarcoma. Both these and the stem cells occasionally exhibited incomplete division with the development of multinucleated cells resembling but not quite identical with those characteristic of Hodgkin's lymphoma. Finally, there was loss of the compact appearance observed in the Type II follicles and instead, a loose edematous structure, the cells of which were separated by clear spaces of varying magnitude in which were found dark staining fragments of apparent nuclear debris. The follicles were somewhat larger than those observed in the preceding types and showed minor variation in configuration manifested by short pseudopod-like projections. Sharp distinction from pulp elements persisted, but the occasional fusion of two or more impinging follicles occurred, with confluence of their contents.

Extensive deformity of the follicles led to the establishment of what has been termed the Type IV lesion. These follicles were quite large, completely irregular, and appeared as interlacing strands of elements entirely similar in cytologic character to those described above. Further atypicality and dedifferentiation were apparent but in no instance was there complete fusion with total replacement and obliteration of structure as was the case in other forms of lymphoma (figure 8). Nodules did appear to rupture occasionally, and in a patchy fashion intermixture of follicular and pulp cells was noted. In several cases follicular irregularity with large sweeping strands often extending through several low power fields presented so unusual an

appearance that identification as follicular lymphoma was difficult. A high degree of polycellularity and the occasional appearance of giant cells simulated Hodgkin's disease but the persistence in part of some follicular structure served to differentiate the lesion. Silver stains offered further differential assistance in this regard, for these demonstrated the persistence and compression of extrafollicular fibrils. Scirrhus Hodgkin's lymphoma, it is true, may exhibit nodular aggregation of neoplastic elements separated from each other by strands of collagenous fibers but despite marked compression of reticulum in the true follicular disease no significant collagenization ever appeared.

These observations of morphologic variation suggest a recognizable histogenic pattern. The four types described represented fairly distinct histologic entities and there was a sufficient degree of overlapping to permit the assumption that each was a different phase of the same basic process. In an attempt to seek clinical confirmation, 41 cases were analyzed with this thesis in view. These were found to be roughly equally divided among the four histologic follicular types. By breaking down the total duration of illness in these cases into the period preceding and that following biopsy it became evident (table 1) that the duration of symptoms before biopsy was

TABLE I

Follicular Lymphoma Type	Duration of Symptoms Preceding Biopsy	Duration of Disease After Biopsy	Total Duration
I	2.0 years	5.7 years	7.7 years
II	3.6 years	3.2 years	6.8 years
III	4.1 years	1.8 years	5.9 years
IV	4.1 years	2.3 years	6.4 years

shortest for Type I lesions, intermediary for Type II, and longest for Types III and IV. The duration of disease subsequent to biopsy, as had been suspected, was longest among the Type I cases and roughly progressively shorter for the remaining types. The total average duration for each group, although not entirely similar, bore a closer relationship to each other than to the other forms of lymphoma. These figures were not altogether conclusive but they did offer a reasonable degree of evidence that the histologic lesions described could represent progressive phases in the development of follicular disease.

Jackson^{5, 6} has suggested that ultimate follicular fusion would produce lesions similar to those of the other types of lymphoma. In eight cases of our follicular series second biopsies (6) or necropsies (2) were made at intervals of two to eleven years after the initial biopsy. The average interval was about six years. Table 2 records the morphologic changes which were encountered and the intervals between the specimens studied.

Five of the eight cases showed changes consistent with the progression of the follicular lesion from an earlier to a later stage. Case III, in whom

no evidence of lymphoma was found at necropsy following death from an unrelated disease, had been subjected four and a half years earlier to a radical surgical excision of a lymphomatous mass in the groin. Since no recurrence occurred this must be considered one of the rare cases in which surgical cure was achieved. Case IV at autopsy showed persistence of a Type IV lesion six and a half years after the original biopsy was obtained. This patient succumbed to massive hemorrhage following irradiation of an epidermoid carcinoma of the cervix. Two other cases not shown in table 2 were autopsied. One died at another institution and was said to have shown generalized lymphoma. We have not had the opportunity of reexamining these

TABLE II
Variation in Histologic Structure

Case	Nature of Material	Interval between Specimens	Type of Lesion	Remarks
I	Lymph node Lymph node	10 years	Type I Type II	Died with lymphoma
II	Lymph node Lymph node	11 years	Type I Type III	Alive with lymphoma
III	Lymph node Autopsy	4.5 years	Type I None	Died, unrelated disease
IV	Lymph node Autopsy	6.5 years	Type IV Type IV	Died, unrelated disease
V	Lymph node Epidural tumor	2 years	Type II Lymphoblastic lymphoma	Died with lymphoma
VI	Lymph node Lymph node	7 years	Type II Type IV	Alive with lymphoma
VII	Lymph node Lymph node	2 years	Type II Type IV	Died with lymphoma
VIII	Lymph node Lymph node	5.5 years	Type II Type IV	Died with lymphoma

tissues. The other patient died as the result of prostatism and was found to have Type I follicular lymphoma in many retroperitoneal nodes, a condition entirely unsuspected clinically. In case 5 alone was there evidence that the theory advanced by Jackson might be correct. In this case no postmortem examination was done, but an extranodal recurrence with the histologic appearance of lymphoblastic lymphoma (lymphosarcoma) appeared two years after an original biopsy showed Type II follicular disease. In spite of this one case, however, at least five of the remaining cases very definitely indicated a progression from simpler to more complex follicular structure as a natural feature of the lesion. The contention that the follicular variations described above probably do represent stages in the pathogenesis of the lesion was adequately supported.

Symmers has described four structural modifications which may occur in follicular lymphoma.⁹ One of these he has termed "polymorphous cell sarcoma," a second was indistinguishable from Hodgkin's disease, a third ultimately developed lymphatic leukemia, and a fourth showed focal follicular necrosis. We have not had occasion to observe the latter type of lesion in any of our specimens but we have seen very similar processes in lymph nodes of patients with acute disseminated lupus erythematosus and Taussig¹⁰ has described somewhat similar lesions in otherwise normal lymph nodes subjected to irradiation. "Polymorphous cell sarcoma" is apparently similar by description and illustration to those changes we have considered representative of advanced (Types III and IV) follicular lymphoma. We are in agreement with Symmers that this represents an end phase of the disease but it is not our opinion that it constitutes a different disease. Several of the Type III and IV lymph nodes, particularly the latter, have exhibited cellular pleomorphism and multinucleated cells simulating the appearance of Hodgkin's disease. In these, however, it has been felt that the presence of follicular residua, the characteristic compression of reticulum, the absence of true fibrosis, eosinophiles, plasma cells, and the dissimilarity of the multinucleated elements from typical Sternberg cells have all obviated a diagnosis of true Hodgkin's disease. None of our cases developed lymphatic leukemia.*

CLINICAL OBSERVATIONS

Records of 507 cases of malignant lymphoma exclusive of the follicular type were consulted for purposes of clinical contrast. Histologic preparations from all of these had been studied and classified variously as Hodgkin's lymphoma (174 cases), Hodgkin's sarcoma (33 cases), lymphocytic lymphoma (118 cases), lymphoblastic lymphoma (76 cases), stem cell lymphoma (42 cases), and reticulum cell sarcoma (64 cases).† Table 3 contrasts the clinical features exhibited by follicular lymphoma with those of the remainder of the malignant lymphomas. The latter were analyzed together without consideration of structural variation, although it was appreciated that the different subtypes varied significantly from one another in many features. Our purpose in ignoring these facts arises from the basic intention of establishing the identity of follicular lymphoma from lymphoma in general.

The great majority of the cases studied were dead and therefore complete information was available. Among the 63 cases of follicular disease, however, only 32 were known to be dead (3 dying of unrelated ailments), 17 were alive and under observation, and 14 were listed as lost although follow-up periods up to five years were recorded.

* Since the submission of this report we have encountered a case of follicular lymphoma with the peripheral blood picture of lymphocytic leukemia.

† The terminology cited represents a nomenclature established on the basis of morphologic criteria as the result of an extensive study of 617 cases of malignant lymphoma. The results of this survey will be published elsewhere by Dr. Tracy B. Mallory and one of us (E. A. G.).

The age of onset, computed on the basis of the earliest symptom attributable to lymphoma, was considerably later with the follicular process. Although the average age of 50 years was also the mean age, 43 per cent occurred between 30 and 50 years and only 7 per cent under the age of thirty. The younger age of initiation of symptoms among the lymphomas (41.7 years) was characterized by a wider distribution throughout all decades. It is thus somewhat unreasonable to consider the follicular lesion an early process from which other forms of malignant lymphoma arise inasmuch as it appears at a considerably later age than the other types of lymphoma.

TABLE III

	Follicular Lymphoma	Malignant Lymphoma (Exclusive of the Follicular Type)
Average age of onset	50.0 years	41.7 years
Onset under 20 years	3.5%	14.0%
Onset over 40 years	72.0%	54.0%
Average total duration	6.0 years	3.0 years
Mortality under 2 years	21.0%	56.0%
5 year survivals	47.0%	19.0%
10 year survivals	11.0%	4.0%
Sex (male : female)	1.2 : 1	2.4 : 1
Obstructive phenomena	46.0%	33.5%
Peripheral edema	28.0%	13.0%
Hydrothorax	21.0%	21.0%
Ascites	21.0%	17.0%
Fever	16.0%	42.0%
Peripheral lymph nodes	89.0%	85.0%
Retroperitoneal lymph nodes	63.0%	48.0%
Mediastinal lymph nodes	29.0%	46.0%
Splenomegaly	33.0%	40.0%
Gastrointestinal involvement	2.0%	14.0%
Genitourinary involvement	5.0%	10.0%
Pulmonary involvement	2.0%	9.0%
Cutaneous involvement	5.0%	21.0%
Discrete bone involvement	9.0%	14.0%
Anemia	18.0%	39.0%
Leukocytosis	7.0%	46.0%
Lymphocytosis	5.0%	34.0%
Atypical cells in blood	9.0%	29.0%
Leukemia	0	18.0%

Total duration was twice as long (6 years) in follicular lymphoma as in the other types (3 years). More than one half of the patients in the miscellaneous lymphoma group had expired during the first two years of their illness, whereas only one-fifth of those with follicular disease died within the same period. In fact, almost one half of these patients lived at least five years after onset, while a bare 19 per cent of the mixed cases survived this period. Of the 17 individuals alive with follicular lymphoma at the present time, the average duration is 6.8 years; those cases which had succumbed had lived 5.2 years.

The proportion of male to female patients, which was 2.4:1 for lymphoma in general, was approximately equal in the follicular group. This ratio may, however, be apparent only, since it is not borne out by the figures obtainable from the literature.

Fever of at least 100.5° F. was a relatively common observation in the miscellaneous group (42 per cent) and hyperpyrexia was not unusual. On the other hand, febrile manifestations were not common in the follicular group and in no instance was a very high figure attained. The possibility of an inflammatory background for these lesions was therefore not strongly substantiated.^{4, 9}

Peripheral lymph nodes were enlarged with roughly an equal degree of frequency in both groups. Mediastinal masses were apparent more often in general lymphoma. Retroperitoneal and mesenteric nodes, however, showed involvement much more frequently in follicular lymphoma and often dominated the clinical picture. A common clinical syndrome consisted of ascites, edema of the lower extremities and scrotum or vulva, and palpable abdominal masses. As might be expected under the circumstances, ascites occurred with a slightly greater degree of frequency in the follicular cases. Peculiarly, among 13 with ascites, 9 of which were tapped, 7 proved to have chylous effusion. In the mixed lymphoma group there were 86 cases with ascites, only 7 of which were chylous. Splenomegaly occurred in one-third of the follicular cases and 40 per cent of the others; not a significant difference.

Cutaneous lesions were distinctly rare in follicular lymphoma. An occasional case showed a few isolated, raised, firm, brownish to reddish nodules. No diffuse lesions (mycosis fungoides) were observed although these constituted a significant proportion of the more common (21 per cent) skin affections noted in the larger group of lymphomas.

Intrinsic lymphomatous involvement of the lung, intestine or kidney was quite uncommon in follicular disease although varying degrees of obstruction as the result of extrinsic impingement upon the intestine, ureters, or air passages were observed. Even this, however, did not compare with the frequency of occurrence in the mixed group. In one instance only was there primary follicular involvement of the intestine without evidence of disease elsewhere and in no other case was the process primary except in lymph nodes. Two cases showed spinal cord symptoms as the result of encroachment by epidural tumor. In two patients there was breast involvement, two had testicular tumors, and in one each there was prostatic and tonsillar infiltration. Icterus appeared once only and was presumed to result from obstruction of the extrahepatic bile ducts by enlarged mesenteric lymph nodes. In all of these the visceral process appeared in the course of the systemic disease and though histologic confirmation was not available, characteristic response to irradiation was obtained. Orbital involvement was not observed.

Hematologic abnormalities were unusual. Anemia (3.5 million red blood cells or less) appeared in 18 per cent of the cases in contradistinction of 39 per cent of those with other types of lymphoma. Among the follicular patients, anemia generally occurred only as a terminal manifestation, and

was thought in some instances to represent the effect of long continued irradiation. Leukemia was not observed, although atypical white cells were present in small numbers in a few cases. Lymphocytosis and leukocytosis were sufficiently uncommon to be considered incidental.

Constitutional symptoms were not prominent features of follicular lymphoma. Recognition of the presence of the ailment usually occurred accidentally or as the result of secondary pressure phenomena. Herpes zoster appeared during the course of the disease in three cases. Four patients suffered from epithelial neoplasm in addition to lymphoma. Two had carcinoma of the skin, one of the cervix uteri, and one of the breast. Active tuberculosis was observed in two cases and the incidence of stigmata of healed disease did not exceed that of the population at large.

It is reasonable to conclude from a clinical point of view that the follicular form of lymphoma varies somewhat from malignant lymphoma in general. The process definitely affects an older group of individuals, it offers a far better prognosis, and remains for the most part limited to lymph nodes. There is considerably less tendency toward actual infiltration of adjacent tissues, metastasis is unusual, and hematopoietic complications not common. Retroperitoneal and inguinal lymph node involvement is quite characteristic, and as a result, edema of the lower extremities and chylous ascites are frequent concomitants.

ROENTGENOGRAPHIC OBSERVATIONS

It was quickly evident that from the pure roentgenologic viewpoint there were no characteristic features distinguishing follicular lymphoma from the lymphomas in general. Most of the lesions noted by this means were readily apparent to routine methods of physical examination and the roentgen-ray findings were therefore merely confirmatory in character. In fact, in many instances roentgenologic studies were not performed since clinical examination sufficed.

For the sake of the completeness of this survey, however, certain observations are at least worthy of enumeration.

Sixteen of the cases showed roentgen-ray evidence of mediastinal masses. These were frequently lobulated and more common in the hilar regions. There was no predilection for either side of the chest and only occasionally were masses visible in the posterior or superior mediastinum. Pleural fluid was visualized in 13 patients and was slightly more common in the left chest. Intrapulmonary processes were observed three times; one of these proved to be tuberculosis, one was apparently bronchiectasis, and a third case was not autopsied but the pulmonary lesion was presumed to be lymphomatous.

Splenomegaly and hepatomegaly were each noted in six cases and in four cases intra-abdominal soft tissue masses were directly visualized. Abdominal films showed displacement of a kidney in four cases and in six there was unilateral hydronephrosis. Both of these observations were thought to

be the result of extrinsic retroperitoneal masses and revision to the normal state was apparent following roentgen treatment.

There was remarkably little evidence of extra-nodal disease. Pressure defects of the gastrointestinal tract were observed in four instances. In two cases intrinsic disease of the intestine was visualized but only one of these was found to be a primary tumor of the ileum at operation. The other represented invasive destruction of the cecum by ingrowing retroperitoneal tumor. Osseous lesions simulating metastatic neoplasm appeared six times and in four there was pathologic fracture. In none of these was there evidence of unrelated tumor elsewhere in the body and all responded adequately to irradiation.

THERAPEUTIC OBSERVATIONS

Except for abdominal or thoracic paracentesis for the removal of accumulated fluid and an occasional case with a single localized lesion accessible to radical surgery, the treatment of choice in practically every case has been roentgen therapy. The basic treatment dose (lymphoma dose) was 600 roentgen units measured in air and derived from a 200 kilovolt generator. The operating distance was usually 50 cm. and the filtration 0.5 mm. of copper and 1.0 mm. of aluminum.

Treatment was administered in great part to regions with glandular enlargement, occasionally to the liver or spleen, and rarely over areas suspected of being the source of symptoms, although no lesions were evident to examination. "Spray therapy" was without perceptible value in our hands in this form of disease. It was therefore utilized infrequently.

Bone and visceral lesions and mediastinal and abdominal lymph nodes, the two latter particularly in the presence of effusion, generally required somewhat higher dosages of roentgens than were necessary to produce remission of peripheral processes. As much as 1200r to 1800r units to each of two fields were occasionally necessary to insure control of lesions. Following adequate therapy in follicular lymphoma, however, effusions often subsided without paracentesis and in several cases no need for therapeutic intervention arose for a year or more. Under similar circumstances hydro-nephrosis secondary to extrinsic ureteral pressure was also observed to recede rapidly. We have also observed bronchiectatic cavities caused by the compression of major bronchi completely relieved by roentgen therapy, both symptomatically and roentgenologically.

Experience with the therapeutic response of individuals severely dyspneic as the result of air passage encroachment has not borne out the traditional dictum that reactionary swelling of lymphomatous processes following roentgen-ray treatment frequently produced exacerbation of symptoms and even asphyxia. In follicular lymphoma immediate and dramatic regression was the rule and no exacerbations were observed. Small initial doses were given, however, as a precautionary measure.

Table IV represents the frequency with which poor results were obtained with irradiation in each of the various types of lymphoma. Lymphocytic and follicular lymphoma exhibited the greatest degree of radiosensitivity, only a rare instance of resistance being encountered. Stem cell lymphoma and reticulum cell sarcoma, although apparently only slightly less radiosensitive, required greater amounts of treatment (900r to 1200r) to obtain equivalent effects. So-called Hodgkin's sarcoma and lymphoblastic lymphoma (lymphosarcoma) not only required higher doses of irradiation but at least one-fifth of the cases failed to respond at all.

TABLE IV
Degree of Radioresistance

Type of Lesion	% Cases Resistant
Lymphocytic lymphoma.....	3
Follicular lymphoma.....	4
Hodgkin's lymphoma.....	8
Reticulum cell sarcoma.....	8
Stem cell lymphoma.....	12
Hodgkin's sarcoma.....	20
Lymphoblastic lymphoma.....	21

Complete records of roentgen therapy were available in only 29 of the 63 cases of follicular lymphoma. For purposes of comparison, 100 cases were chosen from the remainder of the malignant lymphomas. Selection of cases was based upon simple criteria. All had received roentgen therapy, all showed accessible lymph node lesions which could be used for the evaluation of therapeutic results, and all had sufficient follow-up data to permit conclusive opinions. Each had a predominance of lymph node involvement and minimal visceral or extranodal infiltration and therefore assured reasonably fair comparison. Analysis proved that these cases were susceptible to division into three major groups, each of which offered distinct prognostic implications associated with certain histologic variations. There was first the group of 29 cases with follicular lymphoma. The others, in view of the relative degree of malignancy evinced, were divided into an "intermediary" group (50 cases) with lesions classified as Hodgkin's and lymphocytic lymphoma, and a "malignant" group (50 cases) consisting of cases with reticulum cell and Hodgkin's sarcoma and stem cell and lymphoblastic lymphoma.

Grading of radiosensitivity was based upon observations of the response of palpable, visible, or visualized lymph nodes. Such response was determined as follows:

- Excellent: Rapid and complete regression of adenopathy with very long intervals between recurrences.
- Good: Early regression but rapid recurrence.
- Fair: Slow regression, often requiring more than a single "lymphoma dose."
- Poor: Little regression of symptoms or signs.
- None: Progression of disease without abatement under treatment.

Additional features considered were the intervals between the regression of lesions and recurrences, symptomatic relief, and the duration of life after treatment. Figure 9, a composite graph in which all of these factors are considered, represents the character of response of the three groups of lymphoma enumerated above (follicular, "intermediary," "malignant"). Since the majority of the criteria of response indicated above varied in a distinctly parallel manner, they are all combined into a single curve for each group.

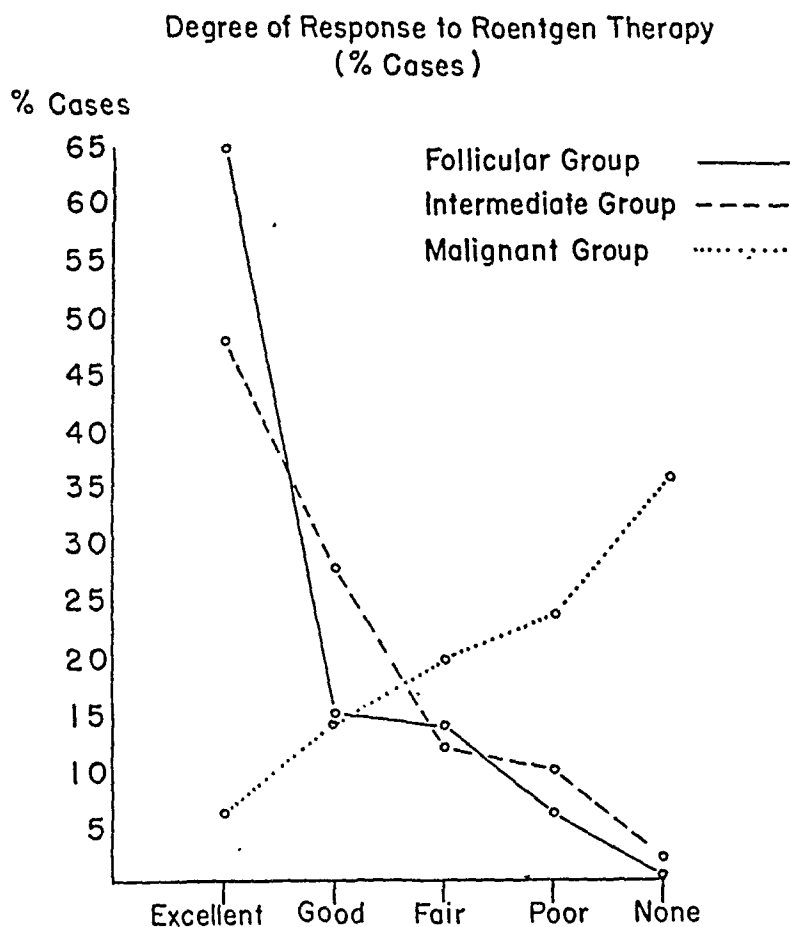


FIG. 9.

The superior efficacy of roentgen therapy in follicular lymphoma is readily apparent. In this category were the greatest number of complete regressions and none failed to improve under treatment. In the "intermediate" group fewer exhibited "excellent" results, and proportionately more showed fairly prompt recurrence of symptoms, but in general the therapeutic course was satisfactory. The "malignant" group showed a very distinct variation, however, the curve of response approximating a mirror image of the other two groups. A relatively high proportion of these cases manifested unimpeded downhill progression of the disease despite radiotherapy.

The incidence and rapidity of local and systemic recurrence closely paralleled the curve of response in the follicular and "intermediary" groups. The "malignant" types of lymphoma, however, varied somewhat unpredictably in this respect.

The duration of the disease following the initiation of therapy was 3.4 years in follicular lymphoma, 3.3 years with the "intermediary" group, and only 0.83 years for the "malignant" lesions. The similarity of prognostic outlook for the first two groups was apparent only, however, since the follicular cases showed symptoms of disease for an average of 2.7 years prior to the administration of roentgen-ray treatment and the "intermediary" group 1.6 years. The prebiopsy duration was even less for the "malignant" forms — 0.76 years. Although patients with follicular lymphoma appeared to survive for a period equal to that of the "intermediary" cases, medical aid was not sought until a much later stage of the disease. It is reasonable to infer that their earlier manifestations were decidedly milder. Furthermore, despite the delayed application of therapy, results were at least as favorable as those obtained in other forms of lymphoma and in most cases even more satisfactory (*vide supra*).

SUMMARY AND CONCLUSIONS

In an attempt to segregate follicular lymphoma from the general group of malignant lymphomas and to establish this disease as a lymphomatous entity a pathologic, clinical, roentgenologic and therapeutic analysis has been recorded.

Histologic studies have shown a distinct variation in structure from that observed in any other type of malignant lymphoma. In only one case was there morphologic evidence of the transition of a follicular process into what appeared to be another form of lymphoma. In all of the others there was abundant evidence, both morphologic and clinical, that certain variations in cellular arrangement and form were representative of a developmental pattern in the pathogenesis of the disease.

Clinical manifestations have been compared with those observed in 507 cases of known malignant lymphoma of varied types exclusive of follicular disease. Certain characteristic features have become evident. Individuals with the follicular process have exhibited initial symptoms at a much later period of life. The prognosis with regard to duration of the disease has been considerably longer with this group than with the remainder of the lymphomas. Constitutional manifestations and visceral involvement have been less frequent, and abnormal hematopoietic phenomena unusual. The apparently greater frequency with which retroperitoneal nodes become involved was impressive and the proportion of those cases with ascites which was chylous in character was considered to be of some diagnostic import.

Since only 29 cases had complete roentgenologic data, it was believed reasonable to select from the other types of lymphoma a sample (100 cases)

in which the clinical manifestations were quite similar to those present in follicular disease. No roentgenographic features with differential diagnostic significance were detected. From a therapeutic point of view the lesions in this form of lymphoma were much more susceptible to irradiation than those of the other groups. Immediate response occurred more frequently, recurrence was much slower in making itself apparent, and in no instance was there progression of symptoms under roentgen therapy.

All of these factors have caused the authors to conclude that follicular lymphoma, although a form of malignant disease of lymphoid tissue, has a distinct identity, with many characteristic clinical and structural features.

REFERENCES

1. BAEHR, G.: The clinical and pathological picture of follicular lymphoblastoma, *Trans. Assoc. Am. Phys.*, 1932, xlvii, 33.
2. BRILL, N. E., BAEHR, G., and ROSENTHAL, N.: Generalized giant lymph follicle hyperplasia of the lymph nodes and spleen, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 669.
3. CALLENDER, G. R.: Tumors and tumor-like conditions of the lymphocyte, the myelocyte, the erythrocyte and the reticulum cell, *Am. Jr. Path.*, 1934, x, 443.
4. EWING, J.: *Neoplastic diseases*, Third Edition, 1928, W. B. Saunders Co., Philadelphia.
5. JACKSON, H., JR.: The classification and prognosis of Hodgkin's disease and allied disorders, *Surg., Gynec. and Obst.*, 1937, lxiv, 465.
6. JACKSON, H., JR.: *Hodgkin's disease and allied disorders. Reports on Medical Progress*, 1940, Little, Brown and Co., Boston, p. 132.
7. ROSENTHAL, N., HARRIS, W., and KEAN, A.: Clinical and radiotherapeutic considerations of follicular lymphoblastoma, *Am. Jr. Roent.*, 1933, xxxiii, 95.
8. SYMMERS, D.: Follicular lymphadenopathy with splenomegaly, *Arch. Path.*, 1927, iii, 816.
9. SYMMERS, D.: Giant follicular lymphadenopathy with or without splenomegaly, *Arch. Path.*, 1938, xxvi, 603.
10. TAUSSIG, F. J.: Effect of irradiation on normal and metastatic lymph nodes, *Am. Jr. Roentgenol.*, 1940, xliii, 539.

ENDEMIC TYPHUS FEVER IN HAWAII*

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INTRODUCTION

A very interesting chapter has been added recently to our knowledge of a world-wide communicable disease, typhus fever. The investigations conducted in the southeastern United States, by members of the United States Public Health Service and by others, have proved that the form of typhus prevalent in this country is a disease separate and distinct from Old World or epidemic typhus. Reports from various parts of the United States and from other countries show large and apparently increasing incidence of the milder endemic form of typhus fever. This, of course, may be merely due to greater awareness on the part of physicians to the occurrence of the disease. Such probably is the case in Hawaii where the disease has been recognized only since 1933, although it undoubtedly was prevalent many years before this. An epidemiological study of the first 163 cases reported to the Territorial Board of Health and a clinical study of 33 local cases personally attended, is herein presented.

HISTORICAL OUTLINE

Brill, in 1898, gave the first clinical description of endemic typhus fever. He applied the newly discovered Widal test to cases having typhoid-like symptoms and found 17 that gave negative agglutination. These cases all had similar symptoms; namely, a short course of fever with sharp termination in from 12 to 14 days and an extensive rash. Dr. Brill¹ continued his clinical investigations and in 1910 reported his findings in a total of 210 cases.

Maxcy and Havens in 1923 reported that cases of mild typhus similar to Brill's disease, occurring in the south, gave a positive agglutination reaction with *Proteus* X₁₉, a test found positive by Weil and Felix in 1915 in cases of epidemic typhus fever.

Maxcy^{2, 3} continued his studies in the southeastern United States and made important observations regarding the epidemiology of endemic typhus. He pointed out that it was a disease of business establishments, particularly associated with grain or food handling places, and not of homes; that it did not select the poor and uncleanly; and that it was not associated with lousiness. He suggested that there existed some rodent reservoir (rats or mice) and that the transmission from this rodent reservoir might be by some insect vector.

The correctness of Maxcy's hypothesis was proved by the researches con-

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ducted by other members of the United States Public Health Service. Dr. Dyer and his associates, Badger, Ceder, Rumreich and Workman ^{4, 5, 6, 7} in 1931 and during the subsequent 12 months, published a series of papers which established beyond doubt the true epidemiology of endemic typhus. They showed that endemic typhus was essentially a disease of rats, and was transmitted from rat to rat, and occasionally from rat to man, by rat fleas (chiefly by *Xenopsylla cheopis*, but also by *Ceratophyllus fasciatus*). They showed, furthermore, that the virus multiplies enormously in infected fleas, and presented evidence suggesting the method of admission of the virus into animals by rubbing crushed infected fleas or infected flea feces into wounds made by bites of the flea or by scratching.

More recent work by Dyer and Brigham ^{8, 9, 10} has shown that other animals native to parts where typhus fever exists in endemic form are susceptible; for instance, mice, woodchucks, flying squirrels and cats. Moreover, infected field mice have been discovered in endemic foci. This suggests that reservoirs other than the rat may be, or may become, important in the transmission of typhus fever in the United States.

EPIDEMIOLOGY

Endemic typhus, according to present day teaching, is one of a group of related diseases caused by rickettsia.¹¹ The following classification by insect vector of the principal rickettsial diseases, is taken from the League of Nations Report on Typhus Fever ¹²:

1. Epidemic typhus fever, human louse-borne typhus, exanthematous typhus, or Old World typhus, is a disease of humans, transmitted from man to man by the body louse. Its greatest incidence is in Central Europe, Asia, Africa and South America.

2. Endemic typhus fever, flea-borne or murine typhus, or Brill's disease, is a disease of rats and occasionally other rodents, transmitted from rat to rat and at times from rat to man by means of the rat flea. This group includes, besides American endemic typhus, Toulon ship-typhus, Hone's disease of Australia, Indian typhus ("Bangalore type"), tropical urban typhus or "shop" typhus of Malaya.

3. A third form of typhus fever is claimed by certain investigators to be alternately louse-borne and flea-borne. Mexican typhus (tabardillo) and Manchurian typhus belong to this group.

4. The mite-borne typhuses include tropical rural typhus or "scrub" typhus of Malaya, mite fever of Sumatra, Japanese river fever (Tsutsugamushi), Indian typhus ("X_k" type), and Queensland coastal fever. The reservoir in this group may be rats or field mice and perhaps birds, and a mite is the vector.

5. Tick-borne typhuses include Rocky Mountain and Eastern spotted fever, *boutonneuse* fever, Kenya tick-bite fever, South Africa tick-bite fever, Sao Paulo typhus, and Minas Geraes typhus.

TYPHUS IN THE UNITED STATES

Old World or epidemic louse-borne typhus fever has never gained a foothold in the United States. The last true epidemic occurred in New York City in 1892-1893. Short-lived outbreaks were reported in New Mexico in 1922 and in Iowa and California in 1917. These last two were imported from Mexico.

A tick-borne rickettsial disease, spotted fever, has been known for a long time in the Rocky Mountain States. It was recognized in eastern states about the time the important epidemiological work on endemic typhus, previously recorded, was reported, and by the same group of investiga-

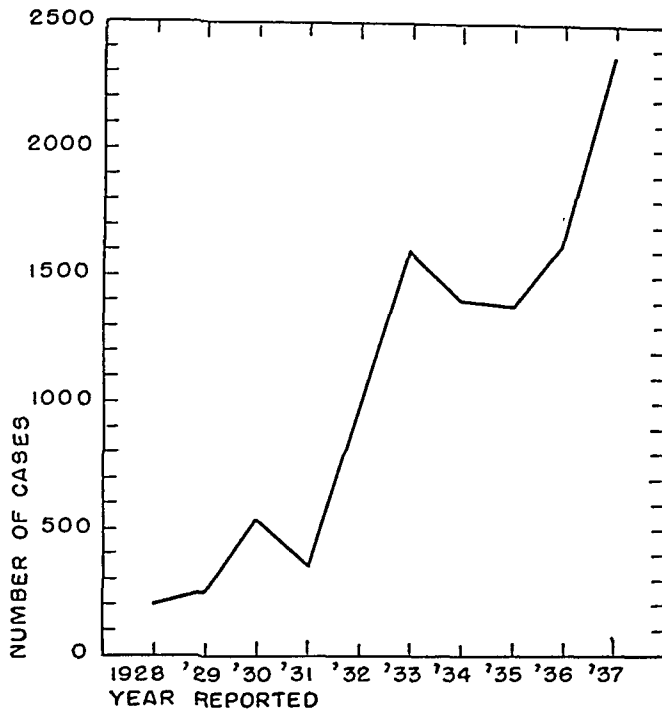


FIG. 1. Endemic typhus fever cases reported in the United States each year 1928-1937. This curve shows a marked rise from some 200 cases in 1928 to 2400 cases in 1937. The first rise between 1931 and 1933 is probably accounted for on the basis of the work of the United States Public Health Service which focused attention upon the disease and brought forth many new reported cases. The later rise, in 1936-1937, may be an index of actual increase in incidence. (Courtesy of the U. S. Public Health Service.)

tors.^{13, 14, 15} The incidence of spotted fever in the United States, according to the League of Nations Report, was 197 cases in 1930; 213 in 1931; 421 in 1932; 467 in 1933; 405 in 1934; and 420 in 1935 (incomplete recording). Principal incidence is in Maryland, Virginia, District of Columbia, North Carolina, Montana, Idaho, Wyoming and Oregon.

Murine flea-borne or endemic typhus shows greater incidence than spotted fever. It is apparently increasing in the United States. This is best illustrated by the accompanying graph (figure 1) showing incidence of typhus in the years between 1928 and 1937.

The greatest yearly incidence of endemic typhus is in three states—Georgia, Alabama and Texas. Moderate numbers of cases are regularly reported in New York, Maryland, Virginia, North and South Carolina, Florida and Louisiana.

The spot map (figure 2) shows distribution of cases in the United States by county, up to 1937. This shows graphically the concentration of cases in the southern parts of the country. Maxcy previously called attention to the urban character of the disease. It more recently has been found also widespread in rural districts as shown by this spot map, and as commented on by Baker, et al.¹⁶

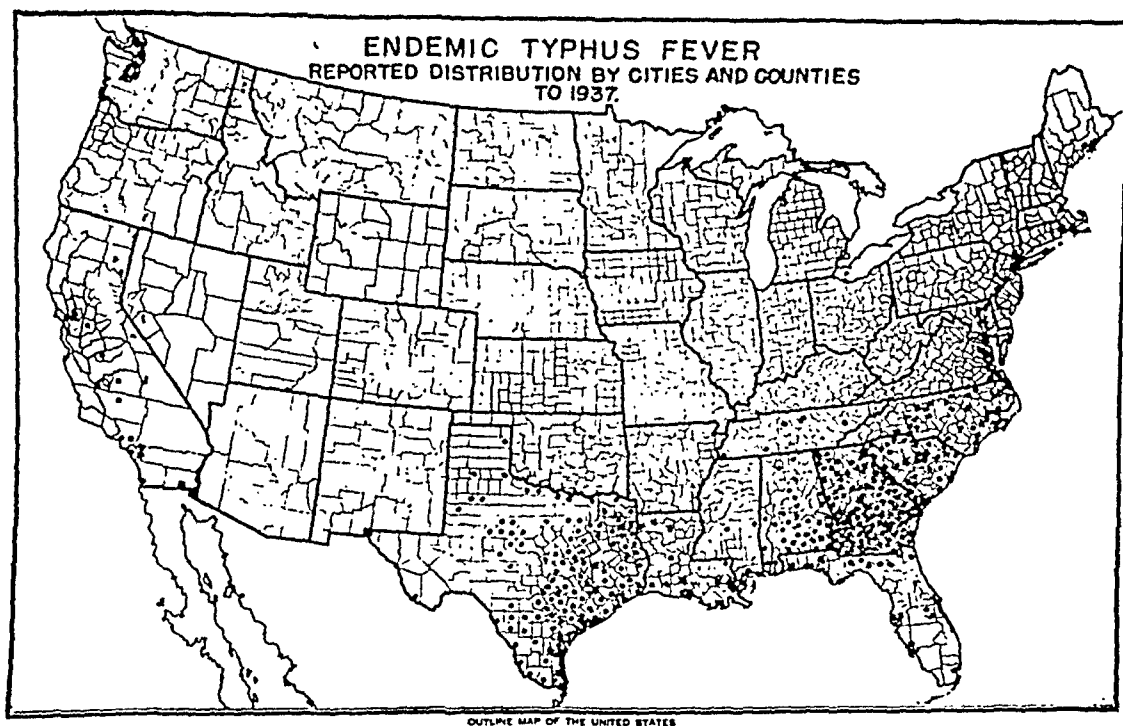


FIG. 2. (Courtesy of U. S. Public Health Service.)

Other important epidemiological features of the disease, as it occurs in the mainland of the United States, are:

1. A sharp increase in prevalence during summer and fall.
2. A relatively low incidence among negroes.
3. A low mortality rate, below 5 per cent in all communities, with the greatest number of deaths occurring in persons over 45 years of age.

ENDEMIC TYPHUS FEVER IN HAWAII

In the fall of 1933, the first case of typhus fever was reported in the Territory of Hawaii. Since that time and up to July 1, 1938, there have been recorded by the Board of Health 163 cases.

The disease undoubtedly was in existence here long before this time. Going back over our cases of mild or atypical typhoid having negative Widal,

shortly after our first case was proved positive, Dr. E. A. Fennel¹⁷ found several from past years with a positive Weil-Felix reaction. It is reported that, as early as 1914, Dr. Jackson diagnosed cases treated in The Queen's Hospital in Honolulu, as having Brill's disease. Dr. Reppun, having attended large numbers of cases of epidemic typhus in Russia, reported a case as typhus fever to the Board of Health in 1921. Several cases similar to his occurred at the same time, and all recovered. It was decided by the authorities that the disease was not typhus fever.

That the disease now occurring in the Territory of Hawaii is actually typhus fever of the endemic type is proved by the following:

Protection tests, with serum obtained from an early case diagnosed as endemic typhus occurring in Honolulu, performed at the National Institute of Health at Washington, proved it to be typhus fever. Dr. Badger produced symptoms typical of typhus in guinea pigs inoculated with brain tissue of a rat trapped on the premises of another diagnosed case. There was thus established a strain in guinea pigs which later was shown at the National Institute of Health to be clinically and immunologically identical with their Wilmington strain of endemic typhus.

The *incidence* of endemic typhus in the Territory of Hawaii by county and by year is shown in the accompanying table obtained from the Territorial Board of Health.

TABLE I
Fiscal Years, July 1 to July 1

	1934	1935	1936	1937	1938	Total
Honolulu City.....	5	18	22	49	28	122
Rural Oahu.....	1	3	2	5	13	24
Total, Island of Oahu.....	6	21	24	54	41	146
Island of Hawaii.....	0	0	0	6	1	7
Island of Maui.....	0	0	7	0	0	7
Island of Kauai.....	0	0	0	0	1	1
Island of Molokai.....	0	0	0	0	2	2
Totals.....	6	21	31	60	45	163

The table shows cases occurring on all the larger islands. However, the majority of cases occur in the City of Honolulu, the only large urban community in the Territory.

Distribution of the first 89 cases reported in Honolulu is shown in the accompanying spot map (figure 3) copied after that of the Bureau of Communicable Diseases of the Board of Health. This map shows wide dissemination of cases. There is well-marked increased incidence over population density in outlying so-called better residential districts, as in Manoa and Kaimuki.

Rats trapped on or about the premises of cases of endemic typhus fever have been found to give positive Weil-Felix reactions. Guinea pigs inoculated with emulsions of fleas (*Xenopsylla cheopis*), combed from trapped rats, have developed certain suggestive febrile reactions and questionable

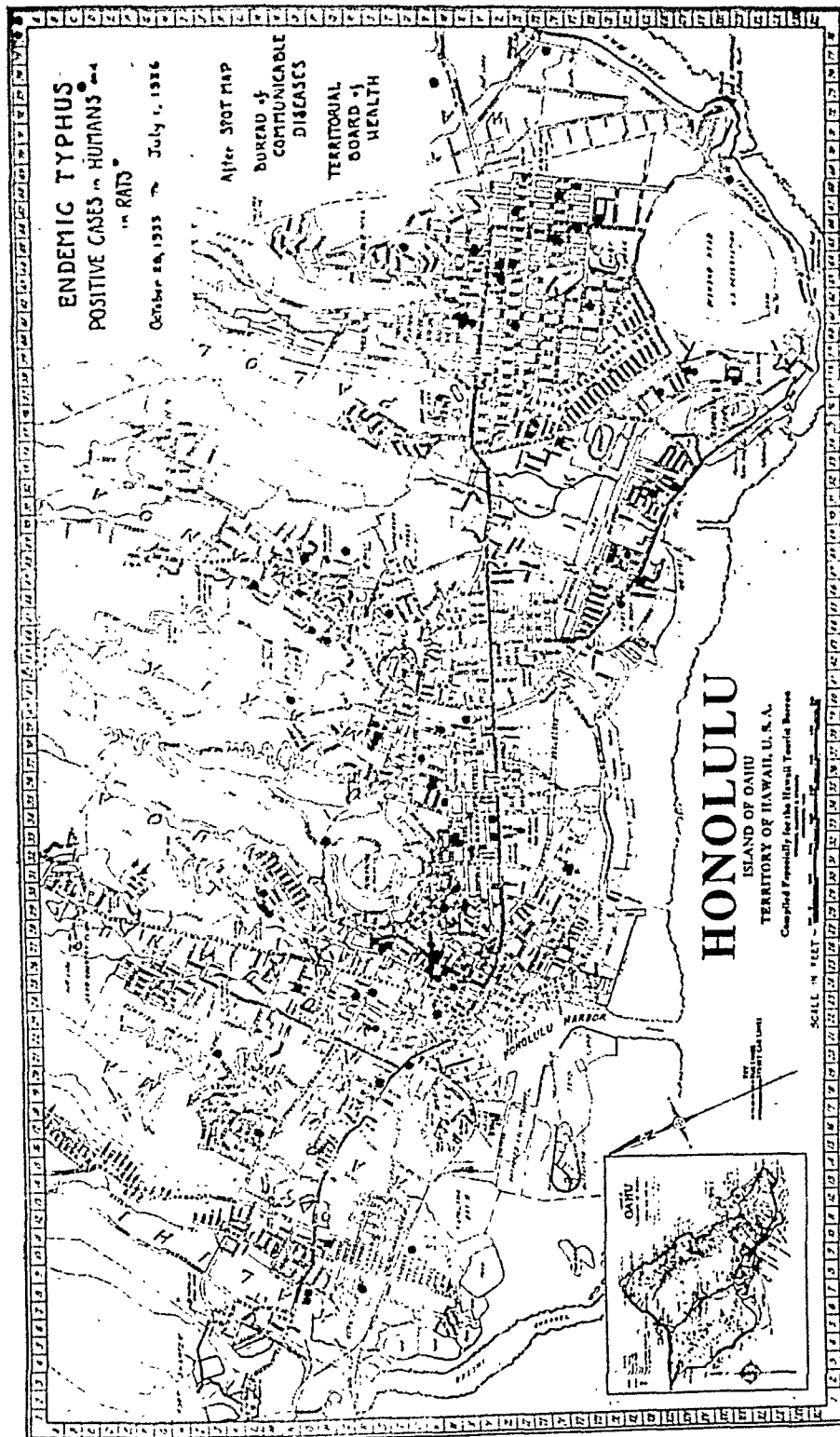


Fig. 3.

scrotal lesions, and their blood serum was reported to agglutinate X_{10} . This cannot be accepted as proof of the existence of the disease in the rats though they were previously accepted as "positive" by the Board of Health. They are so designated on the spot map. There have been six such rats, of which three were *norvegicus*, one *alexandrinus*, one *rattus* and one unclassified. The majority of rats trapped about premises where typhus cases were reported were of the *norvegicus* (brown rat) type. For instance, among 87 rats trapped and classified during the period of three months, 72 were *norvegicus*.

The problem of rat harborage and food supply is a tremendous one in all parts of the city. In residential districts there are stone walls, chicken runs, abundant vegetation, and mango, cocoanut and avocado trees close to dwelling places. On nearby hillsides or vacant lots grow wild guavas, cactus, and other fruit-bearing plants. Complete eradication of rats is impossible.

Segregation of cases by *occupation* was made from reports available in the Board of Health. No predominance among persons engaged in any special type of work was noted. Maxcy, in his early studies of the disease in the southeastern United States, noted high incidence among workers in feed stores and restaurants. The data studied suggest that the most common source of infection in Hawaii is in or about the home.

Age. A study of 156 cases in which age was reported shows distribution by age groups as follows:

TABLE II

1 to 9 years.....	7
10 to 19 ".....	25
20 to 29 ".....	56
30 to 39 ".....	37
40 to 49 ".....	20
50 to 59 ".....	9
Over 60 ".....	2
Total.....	156
Age not stated.....	7
Total reported cases.....	163

The youngest reported case occurred in a child of two years and two months and the oldest in a 70 year old individual.

Sex. One hundred and five of the cases were males and 58 females.

Race distribution is as follows:

TABLE III

Caucasian.....	83
Japanese.....	22
Portuguese.....	20
Part Hawaiian.....	10
Filipino.....	9
Hawaiian.....	8
Chinese.....	6
Puerto Rican.....	4
Korean.....	1
Total.....	163

The composition of the population of the Territory at the mid-period, and the expected and actual numbers of cases of typhus fever for the period from July 1, 1934 to July 1, 1938, are presented in the following table:

TABLE IV

Race	Population*	%	Typhus Cases	
			Expected No.	Actual No.
Hawaiian.....	21,594	5.5	8.95	8
Part Hawaiian.....	37,608	9.6	15.6	10
Portuguese.....	29,863	7.6	12.4	20
Puerto Rican.....	7,470	1.9	3.1	4
Spanish.....	1,261	0.3	0.5	0
Other Caucasian.....	57,069	14.5	23.65	83
Chinese.....	27,495	7.0	11.4	6
Japanese.....	149,886	38.1	62.1	22
Korean.....	6,682	1.7	2.3	1
Filipino.....	53,550	13.6	22.2	9
Others.....	799	0.2	0.3	0
Total.....	393,277			163

* Board of Health estimate for June 30, 1936.

Though actual statistical correlation is not presented, these figures show obvious excess of cases over expectancy in the large group of "Other Caucasians," which is comprised chiefly of American whites. There is a notable reduction in cases over expected numbers among both Japanese and Filipinos. These differences may be due partly to residence. The largest concentration of whites in the Territory is in the City of Honolulu. A larger proportion of Filipinos and Japanese still remain in the rural communities.

A study of the disease by quarters in the Territory of Hawaii and in three states of the United States is presented in the following table:

TABLE V

	1934				1935				1936				1937			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Hawaii	1	1	7	9	1	3	7	17	7	2	10	29	11	2	10	10
Georgia					40	69	219	139								
Alabama					20	51	141	80								
Texas					34	36	94	72								

This table shows that the incidence of the disease in Hawaii rises, as it does elsewhere, in the summer and fall months. The disease tends, however, to have continued prevalence here during the winter months as well.

Up to the present time, only one fatality has been recorded as due to typhus fever in Hawaii.*

EPIDEMIOLOGY AND SYMPTOMATOLOGY OF LOCAL CASES

A. Epidemiology

There is presented herein a study of 33 cases personally attended, in the great majority of instances with complete home or hospital supervision car-

* One more death has occurred in the Territory of Hawaii since the publication of Board of Health reports for the fiscal year ending July 1, 1938.

ried out by the author. A summary of the individual cases is given in the following table.

Data on symptoms, both subjective and objective, laboratory tests, et cetera, are incomplete in many instances. This is because some patients were cared for in the home where observations and laboratory examinations were limited, and also in some instances because of inadequate notes on hospital cases. The small number of cases further limited the value of the tabulation. However, since the review was made by the same person who observed all of the cases, and since the clinical side of the disease was his chief interest, it was felt that the data were worthy of study.

Distribution of Cases. Of the 33 cases studied, 22 were treated at some time during the acute illness in the hospital and 11 were cared for at home throughout the illness. Sex distribution between sexes was almost equal. Seventeen were males and 16 were females. The racial distribution is recorded in table 7.

Age distribution was wide, the youngest case being a child of 10 years and the oldest a man of 58 years. There were 12 cases below 20 years, 14 between 20 and 39, and 7 of 40 or over.

Epidemiological Features. The majority of our cases apparently were exposed to infection about the home. Our patients came from all sections of the city, but more lived in outlying residential districts than in downtown congested areas. Many had good places for rat harborage in chicken houses or stone walls on their lots. Many noted the presence of rats about the premises. In several instances, sick or dead rats were observed or handled. Frequently, several cases were reported in the immediate neighborhood within a period of a few days or weeks. Two families had multiple cases occurring at approximately the same time.

The "B" family lived in an open, rambling house on a dry hillside. The lot was poorly cleared, had chicken houses close to the house and rock piles about. Rats were seen and heard frequently. The first patient in the family became ill on October 2, 1934, and his brother became ill on the seventeenth of the same month. Another case, living less than half a block away across the street and below them on the same hillside, but having no personal communication, was seen October 12, having begun three or four days previously.

In the "J" family there were three cases which occurred at approximately the same time, and there was another case across the street during the same month. The neighbor's cat had recently brought a dead rat on the front porch. The children fondled and played with their own and the neighbors' cats inside and out of the house. The first patient, a girl of seven years, became ill about October 12, 1936, and was first seen on October 17. This same day the mother and brother became ill. Neither of the children had a noticeable rash, but the mother had a typical rash on the fifth day. The boy's illness was quite mild. He was never entirely confined to bed, and fever lasted only a little over a week. All had positive Weil-Felix agglutination tests.

Incubation Period. The incubation period is difficult to estimate. Dyer, Runreich and Badger¹³ say, "In the few cases in which the probable incubation period could be estimated, it varied from seven to fourteen days."

TABLE VI

No.	Date Month Year	Treated Home—H Hosp.* No.	Sex	Age	Race	Symptoms					Temp.		Laboratory						Complications and Notes	
						Onset Acute Pro- dro- mata	Head- ache Day†	Body Aches	Chills	Other	Erup- tion Oc- curred	Max.	Nor- mal	Urine Alb.	Other	Wbc. Thous. Day‡	Polys. %	Weil-Felix Dil./Day‡		Se- verity
1	9/33	Q 81,874	F	58	Port.	+	+ / 10	+	0	Diarrhea Cough	+ / 9	104	19	Tr.	0	10.4 / 10	78	1:5120 / 12 1:320 / 150	Mod.	
2	12/33	H	F	50	Port.	?	+	+	—	—	+ / 7	103 ?	18	++	C & F G casts	—	—	1:2560 / 13	Mod.	
3	7/34	Q 86,960	M	15	Chin.	?	+	?	?	Cough	?	?	?	0	0	7.8 / 22 ?	63	1:2560 / 27 ?	Mod.	
4	9/34	St. F. 7886	M	23	Haw.	?	+ / 14	?	?	—	?	103 ?	20	Tr.	Wbc. + Rbc. +	6.6 / 7	50	1:2560 / 11	Mod.	
5	11/34	Q 88,715	M	26	Jap.	++	+ / 12	++	++	Epigastric pain	+ / 6	104	14	0	—	9.6 / 5	76	1:2560 / 9	Mod.	
6	1/35	H	F	50	Port.	++	+	++	++	—	+ / 7	103	12	Tr.	Wbc. + + Rbc. +	1.8 / 5	64	1:320 / 22	Mod.	
7	6/35	Q 92,535	F	15	P. R.	?	+ / 12	++	—	Muscle pain Hyperaesthesia Vomiting Abdom. pain	+ / 4	104.5	14	+	—	8.9 / 4	84	1:610 / 12	Mod	Secondary anemia
8	10/35	St. F. 9237	M	18	Port.	+	+ / 17	+	+	Epistaxis Chest pain	0	103.8	17	0	Sug. +	9 / 3	72	1:3120 / 15 1:10,240 / 21	Mod	Furunculosis
9	10/35	H	M	15	Port.	+	+	+	+	Chest "constrict- tion," cough and night terrors	?	103.8	?	—	—	—	—	1:2500 / 8	Mod.	Furunculosis
10	10/35	(Brother of 8) Q 94,866	F	30	Cauc.	+	+ / 10	+	—	Abdom. pain Diarrhea	+ / 8	104	15	+	Wbc. + Rbc. +	7.3 / 10	78	1:610 / 12	Mod.	
11	2/36	Q 97,546	M	24	Cauc.	+	?	?	+	Diarrhea	?	104.2	16	0	Wbc. + + Rbc. + +	14.4 / 8	66	1:2560 / 16	Mod.	
12	3/36	Q 97,680	F	20	Port.	+	+ / 12	?	+	Abdom. pain Diarrhea	+ / 8	103.8	16	Tr.	Rbc. + + + Wbc. +	8.3 / 8	56	1:1280 / 12	Mod.	
13	6/36	Q 99,056	M	55	Cauc.	+	+ / 16	+	+	Cough, vomiting, delirium and frequency	+ / 7	105	22	+	Wbc. +	5.9 / 8	80	0 / 9 1:160 / 10 1:3120 / 17 1:20 / 7	Severe	Pyelitis
14	8/36	Q 100,880	F	14	Jap.	?	+	+	—	—	+ / 4	104.2	15	0	0	5.6 / 5	54	1:1280 / 12 1:20 / 10 1:160 / 11	Mod.	
15	8/36	Q 101,012	F	33	Cauc. Haw.	+	+ / 12	+	+	Vomiting Abdom. pain Diarrhea	+ / 8	102.6	15	0	0	7.15 / 3	76	1:320 / 16	Mod.	

* Hosp.—Q—The Queen's; St.F.—St. Francis; C—Children's.

† Day—The day of the illness.

‡ Several cases had repeated blood counts as recorded in table 8 but only one is recorded here

TABLE VI—Continued

No.	Date Month Year	Treated Home—H Hosp.* No.	Sex	Age	Race	Symptoms					Eruption Oc- curred	Temp.		Laboratory						Complications and Notes	
						Onset Acute Pro- dro- mata	Head- ache Day†	Body Aches	Chills	Other		Day*	Max.	Nor- mal	Urine Alb.	Other	Wbc. Thous. Day†	Polys. %	Weil-Felix Dil./Day*		Se- verity
16	9/30	C 13,614	F	10	Cauc.	+	?	?	—	—	+/-	104.8	16	0	—	9.2/6	—	0/7	Mod.	Three cases in the same family	
17	9/30	Q 101,914	F	32	Cauc.	+	+	+	Vomiting	+/?	103.8	16	+	Sug. +	6.7/9	75	1:20/10	Mod.			
18	10/30	H (Daughter of 19)	F	7	Cauc.	?	0	0	0	Fatigue	0	102	?	0	Rbc. +	9.5/9	44	1:640/14	Mild		
19	10/36	H	F	32	Cauc.	+	+	+	—	—	+/-	102	?	—	—	—	—	1:640/42	Mod.		
20	10/30	H (Son of 19)	M	12	Cauc.	?	+	0	—	—	0	?	?	—	—	—	—	1:1280/21	Mild		
21	1/37	Q 103,676	M	19	Jap.	+	+	+	+	Disturbed sleep Epistaxis	0	102	9	+	Wbc. Rbc. F. G. casts few	7.5/4	88	1:160/12	Mod.	Toxic thyroid	
22	1/37	Q 103,817	M	51	P. R.	?	+	+	+	Vomiting Epistaxis	+/?	103.4	?	Tr.	Wbc. few	12.2/7	83	1:2560/?	Mod.		
23	1/37	H	M	22	Jap.	+	?	+	?	Cough Conjunctivitis	0	103	?	++	C G casts few	—	—	1:1280/8	Mod.		
24	7/37	Q 107,814	M	17	Cauc. Chin.	+	+	+	+	Disturbed sleep Cough	+/-	101.6	15	0	0	5.2/6	58	0/6 & 8 1:1280/10	Mod.		
25	9/37	Q 109,222	M	16	Cauc.	+	+	+	+	Conjunctivitis Photophobia	+/-	101.2	19?	0	0	10.7/8	74	0/10 1:1280/14	Mod.		
26	9/37	Q 109,999	F	49	Port.	+	+	+	+	Vertigo	+/-	103.6	16?	0	0	7.8/8	83	1:640/10	Mod.	Toxic thyroid	
27	10/37	H	M	40	Cauc.	+	+	?	—	Chest constrict- ion, vertigo, vom. and diarrhea, disturbed sleep	+/?	102.5?	13?	—	—	—	—	1:640/11	Mod.		
28	12/37	Q 111,474	M	44	Jap.	+	+	+	+	Insomnia Nervousness	+/-	102.8	14	++	Wbc. Hy. casts few	—	—	1:1280/11	Mod.		
29	12/37	H	F	19	Jap.	+	+	+	+	Vomiting Insomnia	+/-	103	16?	—	—	6.2/6	64	1:320/6	Mod.		
30	4/38	Q 114,095	M	17	Fil.	+	+	+	+	—	0	101.6	8	++	Wbc. few C G casts +	10.8/4	88	1:320/11	Mod.		
31	5/38	H	M	25	Cauc. Haw.	+	+	+	+	—	+/-	101.6	17?	—	—	—	—	1:3200/13	Mod.	Toxic thyroid	
32	5/38	H	F	18	Cauc. Haw.	+	+	+	+	Cough	+/-	104	?	—	—	—	—	1:640/12	Mod.		
33	6/38	Q 115,821	F	27	Cauc.	+	+	+	+	—	+/?	104.6	?	+	Wbc. +	7.7	82	1:1600	Mod.		

In one case, C. V. F., this period appeared to be established by the following history: The illness began abruptly just two weeks (14 days) after handling a dead rat. The time was accurately set by checking the day of garbage collection. The patient had found the dead rat in the front yard and had carried it to the rubbish cans which were out in front for mid-week collection.

B. Symptoms

Onset. The onset of the disease, according to Maxcy¹⁸ and to Rumreich, Dyer, and Badger,¹⁴ is usually abrupt. The illness is ushered in with chills or chilliness, fever, malaise, headache, anorexia and prostration. Maxcy recorded abrupt onset in 65 per cent of his series reported in 1926. Blatteis¹⁹ noted gradual onset in 42 per cent of 136 cases studied in 1928. Brill found frequent prodromata of three to four days' duration.

Twenty-two of the 33 local cases studied had an onset which was recorded as acute, while eight cases had inadequate data to record the mode of

TABLE VII

Portuguese.....	7
Other Caucasian (this included one Caucasian-Chinese).....	12
Japanese.....	6
Hawaiian and part Hawaiian.....	4
Puerto Rican.....	2
Chinese.....	1
Filipino.....	1

onset. Three cases had definite prodromata or gradual progression of symptoms recorded.

First symptoms generally were recorded as "flu-like." Headache, body aches, anorexia, chills and fever were the most frequent early symptoms. Headache was recorded in 22 cases, body aches in 18 and chills in 12. Other early symptoms were fatigue, dizziness, constipation, "gas," diarrhea, disturbed sleep or insomnia, sore throat, "tightness of the chest," and cough.

General Symptoms. (a) Headache is recorded as an outstanding symptom by all authors. Brill says, "Headache is one of the most pronounced features of the disease and is almost invariably present." In his series of 50 cases, it was stated to be agonizing in 8, intense in 33, and moderate in 9. He says the headache is general, likens it to the headache of meningitis, and notes rigidity of the neck and positive Kernig occasionally in the most severe cases.

Headache was the outstanding single symptom in our series. It usually occurred at the onset. Occasionally, other general symptoms, tiredness, malaise, and body aches, overshadowed the headache and lasted longer. This was more frequent in younger persons. Headache was recorded as definitely present at some time during the course of the illness in 28 of the 33 cases studied.

The headache was recorded most commonly as frontal, though sometimes it was occipital and sometimes diffuse. The pain was frequently intermittent, increasing greatly in intensity as the fever rose. Ordinarily, the headache persisted nearly as long as the fever. Either it was not present or the duration was not determined in 13 cases. Of the 20 remaining cases, 2 had headache for a week or less, 14 up to two weeks, and 4 over fourteen days.

Relief was obtained sometimes by ice cap alone. Usually, aspirin and codeine combined were required in adults for any degree of comfort. Morphine was given in a few cases at the height of symptoms. A recent case seemed to be afforded relief by hypertonic dextrose (40 to 50 c.c. of 50 per cent solution) administered intravenously, and one case had abrupt cessation of headache following lumbar puncture.

(b) Body aches and pains. Maxcy stated that pains in the back of the neck, lower back, and calves of the legs were common and that general body aches were muscular rather than in joints. In our series, muscular and joint pains were frequent and were more marked than those of other infectious diseases, except influenza. These pains were noted in the extremities more frequently than in the back. The aching pains seemed to be interpreted by children merely as a marked sense of tiredness or fatigue. Rarely a feeling of aching in the chest or abdominal muscles focused attention for a short time on organs of these regions.

Twenty-five of our cases had body aches or pains recorded as a symptom. The duration was shorter than that of headache, usually marked only during the first three or four days. One case, M.G., a 15 year old Puerto Rican girl, had unusually severe body aches, joint and muscle pain and hyperesthesia, persisting to the twelfth day. There was associated in this case an unusual secondary anemia, which may have contributed to the severity and duration of these symptoms.

(c) Chills were frequent but irregular in intensity and in occurrence. Frequently they occurred as a first symptom but were of less startling intensity than those of pneumonia or of malaria. Recurrence was irregular, not daily but perhaps two or three times the first week and once or twice after that in a case of average severity. Chilly sensations were more frequent. Both chills and chilly sensations attended the wider temperature fluctuations which occurred. Twenty of our 33 cases had chills recorded at some time during the course of illness.

(d) Diaphoresis was recorded in 14 of our cases. The sweats occurred irregularly, either related to wide temperature fluctuations or during the stage of defervescence of fever. Sometimes they persisted to the fifteenth day of illness or occasionally longer.

Gastrointestinal Tract Symptoms. Brill stated that constipation was a marked feature of his cases, being present in 42 of 50 cases intensively studied. In two cases, diarrhea followed a previous constipation. Tympanites was not a feature. Maxcy noted "nausea for a few days, followed

by aversion to food to convalescence"; coated tongue, bad breath, and constipation, with a flat abdomen.

Anorexia was present in practically every case in our series and generally persisted as long as the headache and fever. Vomiting occurred most frequently during the early stages of the disease. It was recorded in seven cases of our series. Diarrhea was recorded five times. It consisted of from two to four loose stools a day and abated by the end of the first week. Constipation was a more frequent complaint, particularly during the early stages of the disease. Either constipation or diarrhea was attended at times by abdominal discomfort. This was recorded as a noticeable symptom in eight cases. "Gas" usually was relieved by simple enemata, and distention was never a troublesome feature of the illness.

Respiratory Symptoms. Brill stated that bronchitis was a common accompaniment of the disease.

Cough occurred in five of our cases. In two of these cases it persisted to the tenth and fourteenth days, respectively. Chest pain occurred only as a part of the general muscle aching. Two individuals complained of a peculiar sense of constriction of the chest at onset. Mild sore throat was sometimes present during the early stages of the disease. A definite pharyngeal or tonsillar injection was the only commonly noted physical sign on first examination. Epistaxis was recorded in three cases.

Genito-Urinary Symptoms. Frequency, associated with pyuria, was recorded in two cases. Dysuria was experienced occasionally by patients, but was believed to be due principally to codeine or morphine administered to control the headache.

Central Nervous System Symptoms. Brill emphasized the mental apathy and dulled sensorium as outstanding symptoms but stated that a mild muttering delirium was present only occasionally. Maxcy recorded delirium in 28 per cent of his cases and stated that other symptoms were apathy and mental dullness, increased nervous irritability, and night terrors. Dyer, Rumreich and Badger noted the same symptoms but stated they were much less marked than in cases of Rocky Mountain spotted fever. Delirium, in their experience, was not usually severe.

Increased irritability or depression, insomnia, and unpleasant dreams were fairly common in our experience. True delirium occurred but was not frequent. It was severe in only one case, R. H. W., a 55 year old Caucasian male.

CASE REPORT

R. H. W., 55 year old Caucasian male, was first seen June 27, 1936. He was admitted to The Queen's Hospital on June 29, 1936, and discharged July 13, 1936.

Epidemiological Features. There was a rock retaining wall back of the house, with many rat holes and swarms of rats. The patient also stated that he had noticed rats about his office and made many visits to shops and mills which were rat infested.

Clinical Features. The onset, five days before time of first visit, was manifested by a feeling of general malaise and tiredness. He continued to work until the

evening of the fifth day of illness when his temperature went up to 103°, he became extremely weak and had very severe generalized muscle and body pains. During that night he became delirious. First visit was made the next day, at which time there was a temperature of 104°, and a dry tongue was noted. Rash occurred on the seventh day. This was characterized as macular. It occurred first on the lower chest and by evening had spread to the middle of the back. The next day it had spread over the upper back, then involved the arms, thighs, particularly the inner surface, and by the tenth day it had spread well over the neck, legs, forearms and finally the feet. Rash was extensive and marked, but never became petechial, although the stains of pigment deposit remained for a number of days after the rash cleared.

Course in Hospital. This was unusually severe, and was marked by excruciating headache, and delirium at night. These symptoms continued through the eighteenth day of illness. There were recurring chilliness and diaphoresis. There was some cough and occasional vomiting. Frequency was present after the fourteenth day.

Laboratory Findings. Urine showed 1 plus albumin on the ninth, seventeenth and twenty-second days, with scattered white blood cells. After discharge, there continued to be albuminuria and pyuria, and a cystoscopic examination on July 28 revealed bilateral pyelitis and cystitis, with *B. coli* the causative organism. The white blood cell count on the eighth day was 5,900, with 80 per cent polymorphonuclears, 3 per cent monocytes, 16 per cent lymphocytes. Two days later, white blood cells numbered 4,400, with 86 per cent polymorphonuclears. Weil-Felix was negative on the eighth and ninth days, became positive in a dilution of 1:160 on the tenth day, and on the seventeenth day was positive in dilution of 1:5120.

This was the most severe case observed. The clinical course was marked by high fever, recurring chills, prostration and delirium. A pyelocystitis complicated the case.

Spleen. The spleen was noted as distinctly palpable below the costal margin in 27 of the 50 cases Brill reported. Blatteis found it in 28 per cent of cases reviewed. Rumreich, Badger and Dyer noted it only twice, and Maxcy stated that it was rare. We did not note a palpable, enlarged spleen in any of our cases.

The Eruption. The rash has been well described by Brill, Maxcy and by others. It is a maculopapular eruption. Lesions are small, measure 2 to 4 mm. in diameter, and are dull red or pink in color, irregularly round or oval, having ill defined margins, and fading on pressure. Onset is between the fifth and seventh days of illness. Rumreich, Dyer and Badger said it occurred almost invariably on the fifth day. The site of first appearance is generally the lower chest and abdomen. Spread is to mesial surface of arms, shoulders and back, then to thighs and sometimes lower arms and legs. Involvement of face, palms and soles is extremely rare.

Our cases showed eruption of this general pattern. The intensity and duration varied considerably. No rash was seen in 10 of the group studied. Six of these had too inadequate study to say that there had been no eruption, but four were observed in the hospital from the fourth or fifth day of illness. Not all were dark-skinned individuals.

The time of onset of rash, in our series, was a little later than noted above. In 20 cases where the day of onset of rash was stated, it was first

noted on the fourth day of illness in 4, fifth day in 2, sixth day in 2, seventh day in 5, eighth day in 6, and the ninth day in 1. Ordinarily, the rash disappeared in from four to eight days.

Temperature. Maxcy and Rumreich, Dyer and Badger gave good descriptions of the temperature course. They noted a step-like progression of fever, with usual daily remissions of from one to three degrees, to a maximum on the fifth to tenth day. During the second week, the remissions more nearly approximated normal, the daily rise became less marked, and by the fourteenth day the temperature failed to rise and there was marked relief of symptoms. Defervescence was usually by rapid lysis. Brill reported fall by crisis in 16 cases, by rapid lysis (less than 48 hours) in 17 cases, and by lysis in 17 cases. Brill noted less marked fluctuations of temperature, and stated that remissions usually were less than one degree.

Our cases showed frequent and well marked fluctuations of fever. Sometimes two waves from 99° or 100° F. to 103° or 104° would occur in a single 24 hour period. There generally were wider fluctuations of temperature toward the end of the first week of illness, at the time the rash appeared. The average maximum fever was between 103° and 104°. In 31 cases the maximum recorded temperature was as follows: 102° or less, four cases; 102.2° to 103°, eight; 103.2° to 104°, ten; 104.2° to 105°, nine. No cases had fever over 105°. The maximum was usually reached in the first week, sometimes during the first three or four days. Daily elevation of fever to this degree ordinarily persisted to the tenth or twelfth day, then a rapid or slower lysis occurred, with return to normal by the fifteenth or sixteenth day of illness.

Pulse. The pulse was slow in relation to height of temperature. There was no bradycardia as in typhoid, nor was any unusual character of pulse recorded. The average pulse rate during the febrile period ranged between 80 and 100.

CASE REPORTS

J. A., a Japanese male, aged 26 years, was first seen November 9, 1934, and was admitted to The Queen's Hospital on November 11 and discharged on November 20.

Clinical Features. The patient had become acutely ill three days before the first visit. His complaints were headache, which was severe and throbbing in character "as though his head would burst," chilliness, fever, sweats and dry throat. Lumbar pain had been present at the onset, but none was complained of at time of first visit. There had also been burning epigastric pain and anorexia. Headache and prostration were so severe as to make one suspect meningitis. Neurological examination was negative, nor were there any other abnormal findings except a heavily coated tongue. Temperature was 102° F. at time of first visit. The next two days at home the fever ranged between 100° and 104°. On the sixth day of illness a rash was noted and on this date he was admitted to the hospital.

Course in Hospital. Temperature course (including several temperatures taken at home before admission) is presented in the accompanying chart (figure 4). It shows irregular high temperature persisting through the tenth day. There was a critical drop on this day, but a daily rise to about 100° continued until the fourteenth day.

Laboratory Findings. Urine on the fourth day of illness was negative. Blood count on the fifth day of illness showed 9,600 white blood cells and 76 per cent poly-

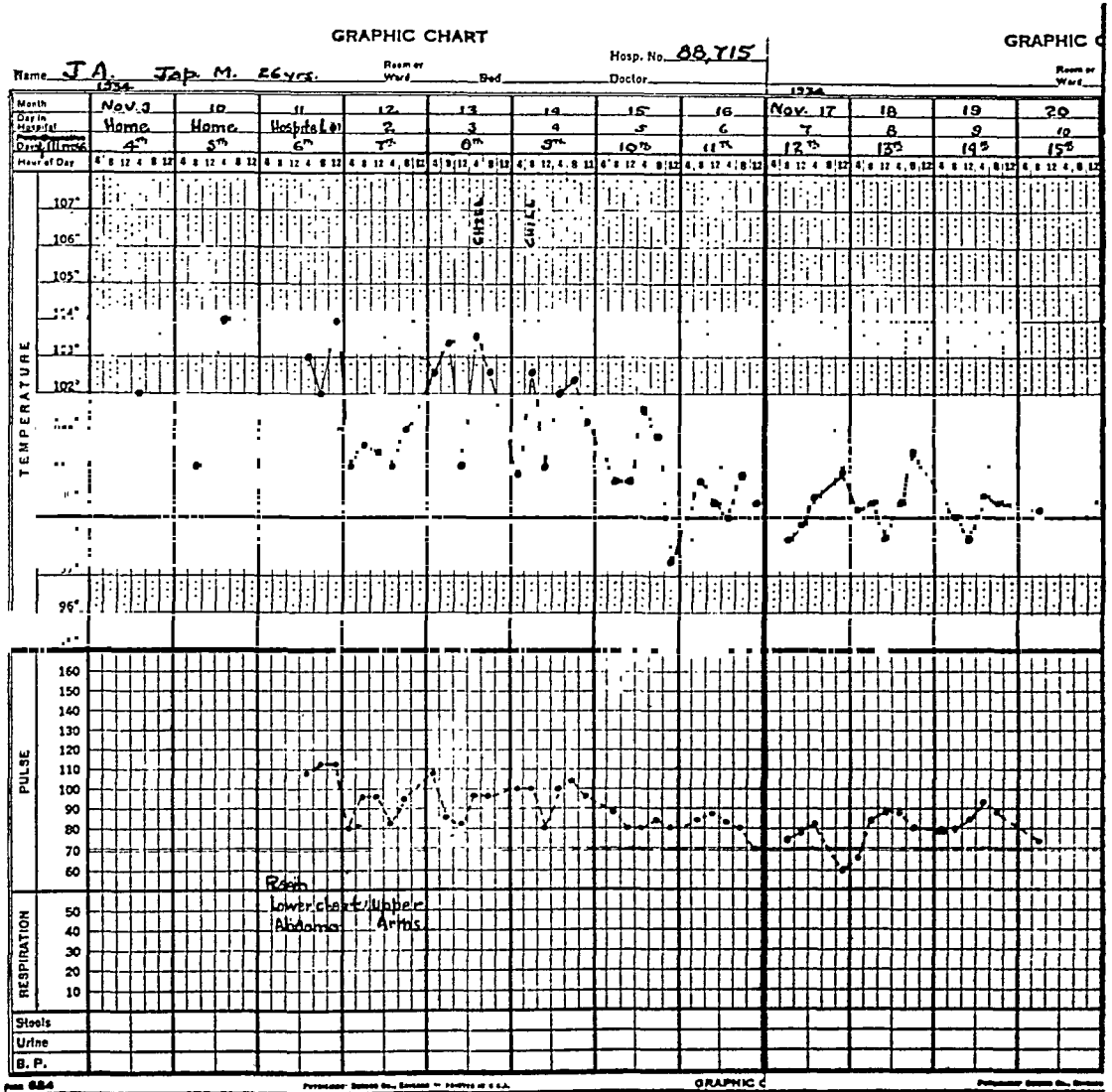


FIG. 4.

A. B., Portuguese male, 18 years old, was first seen on October 4, 1935. He was admitted to St. Francis Hospital on this date and was discharged October 23, 1935.

Epidemiological Features. This was the first of a series of three cases occurring in his immediate neighborhood. The boy lived in a rambling open house on the side

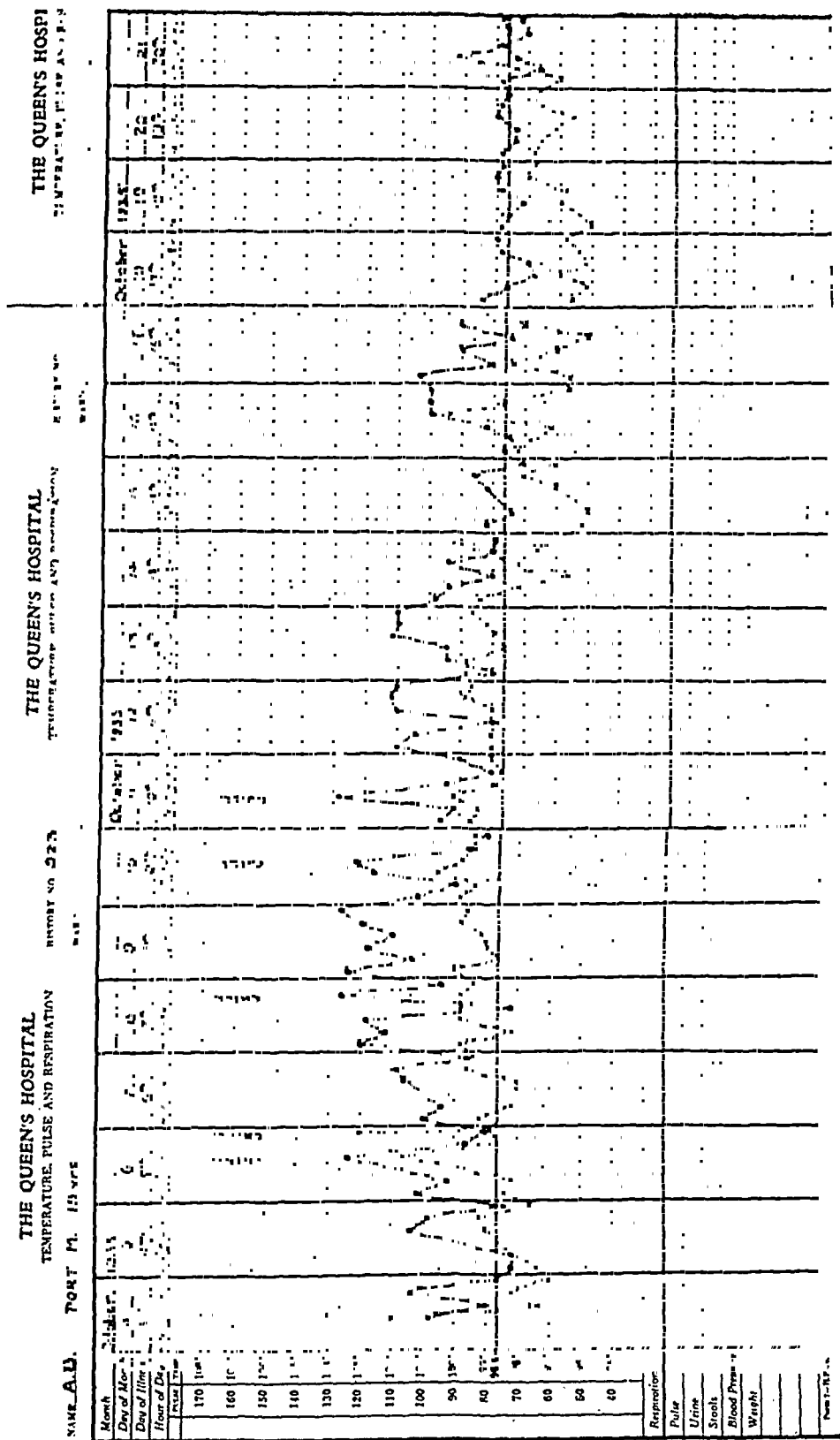


Fig. 5.

of a hill. The family kept chickens, had many birds and animals about the place and there were many rats running around the rocky hillside.

Clinical Features. The onset had been "flu-like," with aching body pains two days before the first visit. His temperature was 101.4° F. at the time of the first examination. Headache was a prominent symptom. Temperature in the hospital was septic, varying between 98.6° and 103.8° up to the tenth day of illness. On the eleventh day and on the twelfth day, the temperature was 102.2° and dropped to 99.6° on the fourteenth day, then fluctuated to 101.4° up to the sixteenth day and on the seventeenth day dropped to 99.4° and did not rise above 99° thereafter (figure 5).

Headache persisted to the sixteenth day, chills recurred irregularly to the twelfth day and diaphoresis was marked through the nineteenth day of illness. There was some abdominal pain and occasional vomiting. Epistaxis occurred twice. A furuncle of the face required opening on the ninth day of illness. No rash was recorded, although examination was made regularly during the hospital stay between the third and twenty-first days of illness.

Laboratory Findings. On the third day of illness, white blood cells numbered 9,000. On the seventh day, white blood cells numbered 6,200 with 68 per cent polymorphonuclears, 32 per cent small lymphocytes. On the thirteenth day, white blood cells were 8,600 and polymorphonuclears 72 per cent. The stool was negative for typhoid and paratyphoid bacilli on the ninth day of illness. Blood agglutination tests for typhoid, paratyphoid A, B, and *B. abortus* were negative on the seventeenth day. Weil-Felix test was positive up to dilution of 1:5120 on this date and became positive to dilution 1:10,240 on the twenty-second day of illness. Urine was negative throughout the course.

C. Laboratory Findings

Urine. The urinary findings were those which accompany any febrile illness. Albumin was recorded as more than a trace in 10 of the 26 cases where this examination was made. When present it usually cleared by the tenth day of the disease. White blood cells in numbers greater than a few occurred in six cases, red blood cells in five, casts in five and sugar in two cases. One case, R. H. W., had albumin and cells persisting into convalescence. A cystoscopic examination in this case showed *B. coli* pyelitis.

Leukocyte Count. Brill noted that there was no leukopenia in this disease, and the average white blood cell count in his series was between 9,000 and 11,000. He noted an average count of polymorphonuclears of 69.4 per cent and lymphocytes 30.6 per cent.

Table 8 records a comparison of distribution of white counts as recorded by Maxcy in 46 cases, and as noted in 40 counts taken on 24 persons in our series:

TABLE VIII

White Count	Maxcy's Series	Our Series
3,000 to 4,900.....	3	2
5,000 to 6,900.....	7	13
7,000 to 8,900.....	20	14
9,000 to 10,900.....	6	8
11,000 to 12,900.....	7	2
13,000 to 14,900.....	2	1
15,000 and over.....	1	0

In our series, the average white blood cell count was about 7,500. Two cases had counts below 5,000. The lowest was 4,400 on the fifth day of

illness. Two were above 10,000, the highest being 14,400 on the eighth day of illness. Several counts made on the same patient (11 out of 24 patients had such repeat blood counts) showed a tendency to drop after the first week of illness.

The polymorphonuclear percentage was commonly between 60 and 80. Percentage of polymorphonuclears in 39 differential counts is shown in table 9. A relatively high ratio of polymorphonuclears occurred early, with later shift toward greater percentages of lymphocytes.

Weil-Felix Reaction. The agglutination of *Proteus* X₁₀ with blood serum of patients usually became positive in diagnostic dilution between the tenth and fourteenth days of illness. Nineteen of 29 cases in which the day of illness could be determined quite accurately became positive within this period. Four became positive before this; one on the sixth day of illness; two on the eighth day, and one on the ninth day. A titer of 1:160 usually is stated to be diagnostic. We usually require a minimum titer of 1:320 for a positive diagnosis by a single test. Still more conclusive is a

TABLE IX

40 to 49%	4
50 to 59%	8
60 to 69%	9
70 to 79%	11
80 to 89%	7
Total	39

rising agglutination titer in repeated tests. Nine of our cases had negative tests or positive in 1:20 dilution on the tenth day or before, and later became positive in diagnostic dilutions of 1:160 or over. Cases frequently had positive tests to the highest dilution set up, i.e., 1:2560 or 1:5120.

Two other strains of *Proteus* organism, X₂ and X_k, the latter known as the Kingsbury strain, were used in Weil-Felix agglutination tests performed on the last three cases. The Kingsbury strain is particularly valuable in differentiating the mite-borne typhuses. In this group, complete agglutinations in higher titers are obtained with the X_k organism and in lower titers with the X₁₀ and X₂ strains. Because of the continuous traffic between the Hawaiian Islands and Japan, the possibility of introduction of a mite carrier was considered. The reactions in lower dilutions, with X₂ and X_k strains and reactions in higher titers with X₁₀, obtained in our cases, are in accord with experience elsewhere in rat flea-borne typhus. Human typhus likewise gives complete agglutination in higher titers with *Proteus* X₁₀ than with both X₂ and X_k strains.

Other laboratory tests were done on these cases, with negative results: stool cultures for typhoid, paratyphoid A, B, dysentery, 11 cases; blood Widal, 14 cases; blood culture, 4 cases.

D. Complications

Complications, in addition to pharyngitis, bronchitis, mild pyuria or hematuria, recorded under symptoms or laboratory data were:

Toxic thyroid, one case (probably present before but aggravated by the typhus); pyelitis, one case; secondary anemia, one case; furunculosis, two cases. No mortality occurred in this series, and only one death* has been recorded in the Territory, as due to endemic typhus.

No particular tendency to special complications is noted by any authors except Brill, who noted regular occurrence of bronchitis. Brill, Blatteis, and Maxcy had a few cases of bronchopneumonia and otitis media. Other rare complications, such as phlebitis and suppurative parotitis, occurred, as they may, in association with any febrile illness.

E. Differential Diagnosis

In differential diagnosis, the following conditions most commonly are considered:

- (1) Upper respiratory infection of influenza type
- (2) Meningitis (lymphocytic chorio-meningitis is particularly to be considered)
- (3) Pyelitis
- (4) Sepsis
- (5) Typhoid fever
- (6) Spotted fever or other members of the rickettsial group may be important in other communities.

The majority of the earlier cases were considered as probable influenza, typhoid or other general infection of unusual type. More recently it has become our custom to suspect typhus when several of the following symptoms present themselves during the first week:

- (1) Persistent and severe headache not relieved by ordinary antipyretics and/or small doses of codeine
- (2) Persistent but irregular fever
- (3) Chills or markedly chilly sensations recurring irregularly
- (4) Abrupt onset of above symptoms, body aches or pains also occurring early
- (5) Irritability, insomnia, night terrors or mild delirium
- (6) Absence of positive physical findings
- (7) Normal or slight increase of white blood cells
- (8) When, in addition to the above findings, a disseminated, fine maculopapular rash,—appearing first on lower chest and upper abdomen and then extending to back, upper arms and thighs,—occurs between the fifth and eighth days of illness, we feel quite certain of our diagnosis.

* One more death has occurred in the Territory of Hawaii since the publication of Board of Health reports for the fiscal year ending July 1, 1938.

The Weil-Felix agglutination test performed on the patient's blood serum becomes positive in diagnostic titer between the tenth and fourteenth days of the disease.

SUMMARY

1. Typhus and the typhus-like diseases (rickettsial diseases) have world-wide distribution.

2. The most practical classification of the diseases distinguishes at least four groups according to insect vector; namely,

- (a) Human louse-borne typhus (epidemic or Old World typhus)
- (b) Murine flea-borne typhus (endemic typhus)
- (c) Mite-borne typhus
- (d) Tick-borne typhus.

3. Endemic typhus fever is a disease separate and distinct from epidemic typhus fever, having milder symptomatology, different epidemiology and low mortality.

4. Endemic typhus is prevalent in certain sections of the United States, having greatest incidence in Georgia, Alabama and Texas.

5. Endemic typhus is also prevalent in Hawaii.

6. Epidemiological features of endemic typhus in Hawaii are similar to those of the disease as it exists on the mainland of the United States. Outstanding among these are:

- (a) High incidence in summer and fall months
- (b) Greater incidence in urban than in rural districts
- (c) Greatest incidence in young adult age groups
- (d) Prevalence is greatest among Caucasian whites as compared with other racial groups. (Japanese and Filipinos have particularly low recorded incidence.)

7. The incubation period is seven to fourteen days.

8. A study of 33 cases personally observed showed a clinical picture similar to that described in cases of endemic typhus in the southeastern United States.

9. The onset is usually abrupt, with chills or chilliness, fever, aching body pains, headache and prostration.

10. Headache continues an outstanding symptom throughout the course of the disease.

11. Irritability, insomnia, night terrors or mild delirium are not infrequent.

12. Gastrointestinal symptoms include nausea and vomiting early, anorexia usually throughout the febrile period, constipation frequently, abdominal discomfort, mild diarrhea occasionally.

13. A palpable enlargement of the spleen, reported by some writers, was not found in our series.

14. Mild pharyngitis usually is seen early in the course of the disease.

15. Fever continues about two weeks, oftentimes with irregular fluctuating curve, reaching a height of 103° to 105° by the end of the first week. Fall is most frequently by rapid lysis. The pulse is generally slow in relation to the peaks of fever. Diaphoresis frequently accompanies wider temperature fluctuations.

16. The rash is characteristic, disseminated, maculopapular and appears usually between the fifth and eighth day.

17. White blood cells average 7,500 and polymorphonuclears range between 60 per cent and 80 per cent.

18. The Weil-Felix agglutination test becomes positive in diagnostic dilutions (1:160 or above) usually between the tenth and fourteenth days of the illness (sometimes by the end of the first week).

19. Complications are rare and mortality very low in Hawaii. In the mainland of the United States a maximum mortality is 5 per cent. Most deaths have occurred in persons over 45 years of age.

CONCLUSIONS

Endemic typhus fever is a disease of sufficiently frequent occurrence in certain communities to warrant consideration from an epidemiological and clinical viewpoint. Such a situation exists in Hawaii and at least parts of the mainland of the United States. In these sections, endemic typhus fever should be suspected in persons suffering from irregular fever and general toxemic symptoms persisting over a week, particularly when headache is intense and persistent, and when a generalized rash occurs about the end of the first week of illness.

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BIBLIOGRAPHY

1. BRILL, N. E.: An acute infectious disease of unknown origin, Am. Jr. Med. Sci., 1910, cxxxix, 484-502.
2. MAXCY, K. F.: An epidemiological study of endemic typhus (Brill's disease) in south-eastern United States, Pub. Health Rep., 1926, xli, 2967-2995.
3. MAXCY, K. F.: Distribution of endemic typhus (Brill's disease) in the United States, Ibid., 1928, xliii, 3084-3095.
4. DYER, R. E., CEDER, E. T., LILLIE, R. L., RUMREICH, A., and BADGER, L. F.: Experimental transmission of typhus fever in the United States by the rat flea (*Xenopsylla cheopis*), Pub. Health Rep., 1931, xlv, 2415-2416; 1931, Ibid., 2481-2499.

5. DYER, R. E., CEDER, E. T., WORKMAN, W. R., RUMREICH, A., and BADGER, L. F.: Transmission of endemic typhus by rubbing either crushed infected fleas or infected flea feces into wounds, *Ibid.*, 1932, xlvii, 131-133.
6. DYER, R. E., CEDER, E. T., WORKMAN, W. R., RUMREICH, A., and BADGER, L. F.: Experimental transmission of endemic typhus fever in the United States by the rat flea (*Ceratophyllus fasciatus*), *Ibid.*, 1932, xlvii, 931-932.
7. DYER, R. E., CEDER, E. T., WORKMAN, W. R., RUMREICH, A., and BADGER, L. F.: The multiplications of the virus of endemic typhus in the rat flea (*Xenopsylla cheopis*), *Ibid.*, 1932, xlvii, 987-994.
8. DYER, R. E.: Endemic typhus fever-susceptibility of woodchucks, house mice, meadow mice, and white-footed mice, *Ibid.*, 1934, xlix, 723-724.
9. BRIGHAM, G. D.: A strain of endemic typhus fever isolated from a field mouse, *Ibid.*, 1937, lii, 659-660. Susceptibility of animals to endemic typhus fever, *Ibid.*, 1937, lii, 660-661.
10. BRIGHAM, G. D., and DYER, R. E.: Endemic typhus fever in native rodents, *Jr. Am. Med. Assoc.*, 1938, cx, 180-183.
11. ZINSSER, H., and BAYNE-JONES, S.: A textbook of bacteriology, Sect. IV, The Rickettsia Diseases, Seventh Edition, 1934, Appleton, New York.
12. Epidemiological Report of the Health Section of the Secretariat, League of Nations, Typhus Fever, January-March, 1936, R. E. 181: 1-16 and July-September, 1936, R. E. 183: 99-160.
13. BADGER, L. F., DYER, R. E., and RUMREICH, A.: An infection of the Rocky Mountain spotted fever type in the Eastern Part of the United States, *Pub. Health Rep.*, 1931, xlv, 463-470.
14. RUMREICH, A., DYER, R. E., and BADGER, L. F.: The typhus-Rocky Mountain spotted fever group—an epidemiological and clinical study in Eastern and Southeastern States, *Ibid.*, 1931, xlv, 470-480.
15. DYER, R. E., RUMREICH, A., and BADGER, L. F.: The typhus-Rocky Mountain spotted fever group in the United States, *Jr. Am. Med. Assoc.*, 1931, xcvi, 589-593.
16. BAKER, J. U., McALPINE, J. G., and GILL, D. G.: Endemic typhus fever, *Am. Jr. Pub. Health*, 1934, xxiv, 1068-1072.
17. FENNEL, E. A.: Endemic typhus fever in Hawaii, *Jr. Am. Med. Assoc.*, 1934, cii, 1135-1136.
18. MAXCY, K. F.: Clinical observations on endemic typhus (Brill's disease), *Pub. Health Rep.*, 1926, xli, 1213-1220.
19. BLATTEIS, S. R.: Endemic typhus fever (Brill's disease); a report of 138 cases, *Med. Clin. N. Am.*, 1928, xi, 1099-1108.

INSIGHT AS AN AIM IN PSYCHOTHERAPY *

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AN old friend of the writer's who recently visited one of the most celebrated medical clinics in the world, recounts with creditable humor the following incident which occurred during the prolonged and elaborate examination to which he was submitted. The patient, pressed by responsibilities of a busy life, had neglected outdoor games and other exercises for many years and at the time of his admission to the clinic weighed 40 or 50 pounds more than a generous allowance for his height and bony framework would grant as reasonable.

After painstaking and prolonged roentgenologic, serologic, metabolic and directly physical procedures, this man, apprehensive but prepared to face the worst, was stripped to complete nudity and led into a circle of specialists. He took his place somewhat diffidently on the metal-topped stool, visible on all sides to the grave and searching scrutiny of more than a dozen pairs of solemn eyes. Some of the faces were lined with age, some bearded; others, though still young, were no less impersonal or less impressive. All kept focused on him an unremitting attention while various members of the circle commented on his pupillary reactions, his abdominal reflexes, his cardiac sounds and other pertinent points. As the examination proceeded the patient was put at his ease by a disarming smile from one renowned medical scientist, a comment fraught with kindly humor from another. Turning at last to a summary of the diagnostic situation these celebrated specialists piled up negative reports in reassuring unanimity and, responding to the patient's obvious manifestations of relief, relaxed their formality. Suddenly the comments began to bear on the patient's physical aspect as a whole, his height and general outline, the thickness of his panniculus adiposus, the sagging protuberance at his mid-section, the masses of fatty tissue that probably gorged his omentum and all but crowded out his intestines, the vast and unnecessary vascular equipment and cardiac exertion demanded by this impressive outlay of useless blubber. The question of whether a man of such proportions would ever pause to think what effect he might have on his marital partner's esthetic or romantic sensibilities escaped in gentle inuendo. The fact was not spared that this able, robust man, still in his thirties, had become seriously disfigured and all but disabled by the useless loading of fat he had allowed his body to accumulate. In cool scientific appraisal with occasional spicings of unmalicious wit the comments played upon the nude and uncomfortable victim.

The gastro-enterologist, who had become genuinely fond of the patient

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during their many previous meetings for diagnostic procedures, deliberately asked the cardiologist, "How many years has it been since we were privileged with such a sight as this, Doctor?"

"Among the six hundred and forty physicians at our clinic" the cardiologist, shaking his head, drily answered, "few appearing in such Pagan nudity would be confused with Ganymede or with Memnon Son of the Dawn. But among us we have no such man as this."

The comments continued for some time, a tone of amiable banter relieving the situation of any serious impoliteness, but still allowing the patient ample opportunity to contemplate his body image in reflection from this encircling battery of distinguished medical observers.

This incident is not related here for its anecdotal value but because the writer seriously considers it an example of psychotherapy. It has, furthermore, proved to be effective psychotherapy. At the present writing, several weeks since the patient's dismissal from the celebrated clinic, he is 14 pounds lighter, feels stronger, happier, more energetic and in every way *healthier* than he had felt for many years. He had no surgical operations. He was given no medicine at all. The advice to lose weight and instructions about how to lose weight by diet and exercise had often been offered by physicians in the past. This patient had verbally and perfunctorily agreed; but he had nevertheless made no serious effort to change his habits of life. Progressive loss of endurance, vague but persistent cardiac and gastrointestinal symptoms, a diminishing sense of well-being had driven him to fear serious organic illness and in consequence to live in uneasiness and dread. The seriousness of his situation led him to travel nearly 2,000 miles at considerable sacrifice of time and money for examination and treatment at the great medical center. Though this patient got neither medicines nor operations the writer maintains that his pilgrimage was not made in vain.

What did the patient receive that convinces us his money and time were well-spent? The answer is very simple. He got insight. This new knowledge of himself which we choose to call insight consisted in this case of a real awareness: (1) Of his body as it appeared to others, (2) of the physical and physiological handicaps of a body all but overwhelmed with excess fat, (3) that his body could be relieved of this burden by simple measures demanding reasonable persistence but no very great effort or deprivation on his part. It is perhaps not too much to say that this patient's resistance to a real and conscious awareness of his body-image, an awareness in the sense of Schilder's formulations,¹ was overcome and, seeing himself from this aspect as he really was, he at once set about changing his body. With these changes the body became not only more healthy and effective but, more acceptable to himself as well, even a source of pride and satisfaction in that composite of self-awareness or consciousness in which we all experience life as psychobiologically integrated entities or personalities.^{2, 3}

Whatever school of psychotherapy one may favor and whatever type of presenting symptoms one may have to deal with, no aim is more funda-

mental than the aim of helping the patient gain insight. Nor is any aim more ambitious. The case cited above is hardly one that would be regarded by most physicians as a psychiatric problem at all. The patient, an intelligent and apparently a well-adjusted person, was, of course, free from any sign of a psychosis. There were no discernible physical or personality symptoms that even a very imaginative psychiatrist could say were directly psychogenic in the ordinary sense. Yet it cannot be denied that the one significant factor in his rapid progress towards regaining vigorous health is his gain in insight. One might object and say that the real factors are his changed dietary habits and his new program of recreation and exercise. These, however, are plainly secondary. They had as a matter of fact, been prescribed often in the past. The patient himself freely admitted their advisability. Yet he did not adopt them. And the only possible reason why he did not adopt them is because he did not really see or feel with emotional conviction their desirability and their importance. Or, we might say, he did not feel this sufficiently.

Laymen and even physicians uninterested in psychotherapy might insist that it is strange, or even preposterous, to maintain that a patient of good intelligence is unable to appreciate the necessity of such measures as dieting and exercise in the case just mentioned. Such skepticism, however, does not invalidate the simple fact that this patient did not appreciate this necessity and that the failure to appreciate it, in any sense that has real meaning, is proved by his failure to do anything about it.

To physicians interested in psychotherapy this astonishing inability of normal and even of extremely intelligent persons to see obvious factors in their life situation is as familiar as the morning sunlight. The child who is a feeding problem often enough has a mother who nags at him through every meal, cajoling, teasing, threatening and often losing her temper in frantic attempts to make him eat. The most subtle dialectic and the most impressive citations only too frequently fail to persuade such a mother to leave her child alone at meal times even for a day. The physician assures her that the child's failure to eat is because he is so harassed and overpersuaded that the food loses its savor. The mother often agrees with the physician but continues in her activity. The patient who consults a dozen different physicians each year vainly seeking a cure for constipation which has made his life a misery for twenty years will usually be deaf to all explanations that the many and powerful laxatives with which he alternately scourges and paralyzes his bowel functions are a very important factor in the causation of his disorder. The neurotic drinker who loses his digestive powers, many excellent positions in business, his standing in the community and most of the pleasures of life is not easy to convince that the excessive drinking, which usually has ceased to give him any of the satisfaction which ordinary social drinking gives, is itself a very important factor in causing the situation which he vainly seeks to escape by drugging himself with drink. This neurotic drinker will often agree verbally, and will think that he really

agrees, but he does not see in the sense of seeing with emotional conviction, and so he does not actually agree. If he did see and agree he would stop drinking. The old adage that one should judge a person's intentions or convictions by his actions rather than by his words is theoretically understood even by middle grade morons* but in practice many scholars and scientists of high repute show no grasp of its meaning.

Insight into such problems as those mentioned is not easy for the patient, however great his intelligence, in any true or useful sense. In the more readily apparent psychiatric problems manifested in the classical psychoses and psychoneuroses a loss of insight is more obvious.

In psychasthenia, for instance, a vivid and persistent fear of contamination may cripple the patient's life, making it all but impossible for him to open doors without first wrapping the doorknobs in sterilized cloths, causing him to shrink in genuine disgust from the touch of a lovely woman's hand since he realizes that her hand may have touched a fence post that had been touched by someone else who had shaken hands with a person who, in turn, had been in contact with someone suffering from an infectious disease. It does little good to assure such a psychasthenic patient that there is no appreciable danger of catching this particular infectious disease even by direct contact with the sufferer, or to point out that the causative microorganisms normally dwell in the psychasthenic's own body and in the bodies of other people physically sound. The psychasthenic often knows all this. He is aware that his fears are not grounded in reason. Nevertheless his fears torment him; and if he tries to ignore them he is overcome with disabling anxiety.

In such cases it is not always easy for the physician to discover what is really causing the patient's fear and how his life-pattern came to be constructed in such a fashion. Is it a fear of sexual or aggressive tendencies in the patient, unrecognized by himself and inconsistent with his conscious ethical standards? Did the exaggerated fear of masturbation or ideas of moral uncleanness born of silly parental ideologies drive him in compensation to symbolize thus his struggle for a hypothetical purity? Can the fear of contamination be traced back to a simple beginning where over-severe and nervous parents demanded too much of the patient as a child in training him to control his excretory functions? Did he as a result of this meet his next problem feeling that he must strive to exceed his actual abilities and sense himself doomed to failure? Did he gradually become overscrupulous in all things under the continuous effort to avoid failure (and especially contamination or dirtiness) by exaggerated procedures? Could the cumulative experiences of life have so shaped him that he must as he stands, almost mechanically and whether he chooses to or not, always struggle, even by fantastic compulsive rituals, to avoid dirt and infection or what is symbolized for him by them?

* This question is placed in the ten year group in the Binet Stanford Psychometric test and is answered correctly by the average child of 10 years.⁴

Even if the physician is able to see the background of such a patient's symptoms the patient himself cannot be made to gain real insight into this whole life scheme by a statement from the physician explaining it. In such cases many months of treatment are often necessary; months during which the physician, whether by the free association methods of classical psychoanalysis,^{5, 6} the more direct approach of distributive analysis and synthesis,⁷ of individual psychology,⁸ or by some other approach seeks to lead the patient to understand his symptoms and what lies behind them. To understand this he must understand himself better, must see and admit motivations that he has not been aware of or admitted to himself; or if one prefers so to state it, which he has not fully appreciated.

Why is it so difficult for patients who suffer with psychoneurotic symptoms to gain this insight? The naive conception of an intelligent person, and many psychoneurotic patients are far above the average in intelligence, takes for granted that he can see ordinary facts when they are carefully demonstrated to him and that, seeing them, he will act on them to his best interests. To demonstrate the fallacy of this conception we need not leave the realm of ordinary life.^{9, 10} Everyone has known what it is to reason with a person who we say has a strong prejudice. Whether this prejudice lies in theology, politics, literature or the fashions in women's clothes, we find it uniformly difficult to modify by ordinary reasoning.¹¹ We also find that the person is unaware of having a prejudice and that he cannot be made to admit our accusation. Indeed as the argument progresses, if we have much capacity for insight, we may begin to wonder who has the prejudice, ourselves or the other fellow. For the purpose of our illustration it matters little with whom the prejudice lies or whether both have prejudices which conflict. To make this point more emphatic one need only mention the various religious sects and political parties with their strongly contrasting beliefs and the intelligent persons in all of them who cannot understand their neighbors' beliefs in contrary doctrines. Or one might imagine a discussion of art between an ardent surrealist and a typical member of the British Royal Academy.¹²

What we know as a prejudice maintains itself against ordinary argument and demonstration which fall off like water on a duck's back⁹ leaving it undisturbed if not actually strengthened by its successful resistance.

Why does the prejudice maintain itself so stubbornly? Perhaps if we consider the miser, a familiar character in any community* some simple reasons may become apparent. The miser often has ten times as much money as he could use, even if he should change his ways and live extravagantly; yet he goes threadbare, lives in a wretched environment, denies his children ordinary privileges and sometimes even restricts his diet beneath the requirements of adequate maintenance. But what logician can convince him of the absurdity in his life scheme? Who can make him see that he has

* For a convincing and detailed picture of the miser's personality picture the reader is referred to George Eliot's *Silas Marner* and to Arnold Bennett's *Riccyman Steps*.

no need to hoard more money which he will never use? If such a suggestion is made he is likely to explode in wrath. Even if he consents to discuss the question he will use elaborate casuistry which the observer recognizes as being designed (unconsciously) to maintain the miser's own convictions in the necessity of hoarding. However ingenious this casuistry may be it does not convince anyone but the miser. Of course it is he himself whom this casuistry is designed to convince.

A few simple and superficial reasons why the miser cannot see his folly are perhaps obvious: (1) He has invested years of effort and has suffered much in deprivation to fulfill his unhealthy scheme of life. If he should realize its uselessness he would have to see that he had wasted all this effort and suffering. No one cares to see a heavy investment become worthless. A fundamental biological factor, the tendency to avoid pain or hurt, stands behind his protective blindness. (2) He would have to admit that he had for years been a miser, that he had been wrong thousands of times when he so confidently believed and proclaimed himself right. It is distressing to lose face,¹³ and to see oneself as having been entirely silly where one thought oneself particularly wise, to face the fact that a major source of pride has been a persistent folly. (3) He would have to change all his habits. Habits are notoriously hard to change and any changing is most uncomfortable. (4) The ordinary pleasures of life have usually lost their appeal since he has denied himself for so long that he cannot imagine immediately what delight they give others. They seem obvious to others as an influence to make him give up his miserliness, but to him they are, so long as he remains a miser, invisible and, so, non-existent. (5) He has, through his long practice of miserliness, come to find a kind of pleasure in self-denial, as well as in hoarding. This pleasure is very real though difficult for the ordinary man to understand. One need only cite such examples as the flagellants¹⁴ who choose to have themselves scourged, the Hindu Fakirs who sit for years on seats of sharp nails, or the sexual masochists^{15, 16} who delight in being spat upon, betrayed and otherwise humiliated no less than in being physically beaten by their love objects, to illustrate how readily man can learn to love what is commonly regarded as distressing.

There are reasons then why the prejudice is maintained against the appeals of logic. There are also reasons why the psychoneurotic patient and even the psychotic patient fail to gain the insight which is so important for them to become well. The reasons are often similar. The psychoneurotic patient also dreads to lose face. He may be gaining an unnatural and morbid sort of pleasure from his illness. To see his life-scheme and his hitherto unperceived motivations would cost him pain, shame and great inconvenience. He also has frequently lost the ability to understand the satisfactions of healthy life.

Sherrington,¹⁷ in speaking of organic neurological disorders, has said, "Again in life's final struggle the chemical delicacy of the brain-net can make

distress lapse early because with the brain's disintegration the mind fades early—a rough world's mercy toward its dearest possession." In such situations as that of the miser or the psychasthenic patient we cannot yet detect organic or biochemical changes in the brain. Even if such changes should some day be discerned and measured it would be difficult to prove they arose otherwise than as a result of a certain way of living. In these conditions which we may for the present call psychogenic one sees the same broad biological principle, a mercy towards self, which Sherrington points out in actual brain damage. Such mercy, like euthanasia, we must agree is good when destruction is inevitable. It is, however, inopportune and even tragic if this loss of insight prevails in remediable situations. For then it is loss of insight itself which becomes the physician's most serious problem. To the somewhat imposing question of why an intelligent person should lose the very capacity which would enable him to solve his problems, one might then be justified in answering that it is lost through an untimely and a too ready use of a capacity as intrinsically biological as respiration or the vomiting reflex. Vomiting itself, a most useful mechanism for the preservation of the organism, may become its means of destruction by depleting the body chlorides in remediable situations.^{18, 19, 20} And may not one properly add here that the human organism has for its defense many useful mechanisms, conscious and unconscious, which under certain conditions escape voluntary control, or their own status in the involuntary organization, and, blindly overdoing their originally useful function, destroy what they were designed to serve. What is more essential to healthy living than courage? Yet has not blind courage led dogs into fatal encounters with porcupines and numberless Don Quixotes uselessly into the arms of inoffensive windmills?

Insight has been stressed as the factor of primary importance in psychotherapy and the writer believes that this importance can scarcely be exaggerated. It is at insight that the psychiatric illness must strike in order to exist and to maintain itself. Insight is, however, often difficult to gain. Sometimes it cannot be gained no matter what psychotherapeutic efforts are exerted. It is not difficult to see that the process of gaining insight is usually for the time being extremely unpleasant. So too is the lancing of a boil. If insight should come too suddenly some psychoneurotic patients might be overwhelmed with their situation and attempt suicide or suffer the personality dissolution known as a psychosis. In the plainly somatic branch of medicine, surgery, over zealous and peremptory efforts to eradicate a focus of infection may cause fatal septicemia. If, for instance, the psychasthenic patient who avoids contamination so scrupulously, should suddenly realize that it is not really dirt he fears but homosexual tendencies of which he has been unaware, the stress of facing his situation might be disastrous. In cases of serious psychoneurotic illness, therefore, the patient should acquire insight gradually as he gains enjoyment in the ordinary exercises of life, as he finds activities in which he can lose himself and accomplishment in

which he can take pride. It may be necessary for him to build positively some edifice for his personality before he can abandon the old dwelling of his illness.

Often the psychoneurosis, like the miser's way of living, has so restricted the patient's existence that he has, one might say, nothing else to fall back on. It is therefore important to persuade the patient to change his habits, to enlarge his scope of activities, to break the pattern of his unhappy existence as soon as possible. Even the simplest expedients are often useful. A regular hour for going to bed and for arising, simple calisthenic exercises before breakfast, a carefully selected program of reading, definite social activities at stated times, a walk each evening in the sunset during which the patient tries to keep his attention entirely on what he sees and hears about him, plans for each night in the week which must be carried out whatever his inclinations: such a new routine is often valuable in breaking the old pattern of life in which the psychoneurosis flourishes and may help the patient find himself naturally in existence with others as he works to understand himself.

If the patient can be induced to start normal living in even one obscure corner of his map of life the biological tendencies that make for health may find a foothold. The patient will often object to any planned activity giving many elaborate reasons why he cannot adopt each suggestion. He must be persuaded to go on blindly with new activities whether or not they seem, for the time being, pleasant or helpful. Mere logic, however invulnerable it may be, will seldom induce the patient to follow the physician's advice. What then will induce the patient to do so? There is perhaps no way in which an answer can be given briefly. The degree of the physician's real understanding of the patient, the intensity of the physician's interest in the patient as a human being, everything that the physician has felt and enjoyed and suffered in life and living, no less than the physician's measurable technical knowledge, will influence this issue.²¹

Psychotherapy is often difficult and many of its problems call for considerable patience, wide experience, systematic training and a type of concern with people as personalities which cannot readily be taught. It is nevertheless true that the physician in general practice often overlooks simple opportunities to help patients with psychiatric problems.²² Sometimes only a little time and effort are needed to bring about real improvement in the patient's health and happiness. An interest in personality problems is the most important factor in enabling the general practitioner to seize these opportunities and to make himself more useful to his patients.

SUMMARY AND CONCLUSIONS

1. Psychotherapy has often been regarded by other branches of medicine as an isolated if not a metaphysical or even an occult and unworthy art. It is here maintained that such differences arise from limitations of viewpoint.

The fundamental biological strivings, whether the organism is confronted with a painful furuncle or with an errant bride, have something in common.

2. Even the most obviously somatic medical problems often have a readily demonstrable personality factor; and this factor is sometimes fundamental.

3. The loss of insight, which in some degree accompanies all personality disorders, is the fundamental problem in therapy. This loss is not always replaceable but efforts directed toward improving insight are the primary and logical aim of a reasonable psychotherapy.

4. Biologically there is nothing more abstruse or mystical in this aim than in the surgeon's aim of aligning the angulated bone fragments in a comminuted fracture. Practically the problem is often more difficult. This degree of difficulty may be at times discouraging but should not be an excuse for losing interest.

5. The misunderstanding and even the mistrust of psychiatric methods by the average physician has for years been recognized. The psychiatrists, with their formidable terminologies, their elaborate and sometimes conflicting ideologies, are perhaps responsible, in part at least, for this misunderstanding and mistrust. The importance of expressing psychiatric aims in terms consistent with ordinary medical thinking has been recently emphasized.^{23, 24} This presentation of homely personality problems in simple terms is intended as a small effort in affirmation of psychiatry's unity with medicine in general.

REFERENCES

1. SCHILDER, PAUL: Psychotherapy, 1938, W. W. Norton Co., New York, pp. 25-48.
2. MEYER, ADOLF: Objective psychology or psychobiology with subordination of the medically useless contrast of mental and physical, Jr. Am. Med. Assoc., 1915, lxxv, 860-863.
3. DIETHELM, O.: Treatment in psychiatry, 1936, Macmillan Co., pp. 1-19, New York.
4. Terman, LEWIS M.: The measurement of intelligence, 1916, Houghton Mifflin Co., Boston, pp. 268-272.
5. FREUD, S.: New introductory lectures on psychoanalysis, 1933, W. W. Norton Co., New York.
6. FENICHEL, O.: Clinical psychoanalysis, 1934, W. W. Norton Co., New York.
7. DIETHELM, O.: Investigations with distributive analysis and synthesis, Arch. Neurol. and Psychiat., 1936, xxxv, 467-486.
8. ADLER, A.: The practice and theory of individual psychology, 1927, Harcourt Brace and Co., New York.
9. HART, BERNARD: The psychology of insanity, 1939, Macmillan Co., New York.
10. FREUD, S.: The psychopathology of everyday life, 1924, Macmillan Co., New York.
11. CLUTTON-BROCK, ARTHUR: Evil and the new psychology, The Atlantic Monthly, March 1923, pp. 298-308.
12. BULLIET, C. J.: Apples and madonnas, 1930, 3d Ed., Corvici Friede, N. Y.
13. WOLFE, BERAN: Calm your nerves, 1933, Farrar and Rinehart, N. Y.
14. MENNINGER, KARL: Man against himself, 1938, Harcourt Brace and Co., New York, pp. 87-143 and 248-285.
15. KRAFT-EBING, R.: Psychopathia sexualis, 1924, Physicians and Surgeons Book Co., N. Y., pp. 131-213.
16. v. SACHER-MASOCH, LEOPOLD: Venus in furs. Privately printed in New York, 1928.

17. SHERRINGTON, C. S.: The brain and its mechanism, 1934, Cambridge University Press, p. 24.
18. WRIGHT, SAMPSON: Applied physiology, 1937, Oxford University Press, pp. 562-563.
19. HOMANS, JOHN: A textbook of surgery, 1936, Charles C. Thomas, Baltimore, pp. 928-929.
20. WANGENSTEEN, O. H.: The therapeutic problem in bowel obstructions, 1937, Charles C. Thomas Co., Baltimore, Md., p. 7.
21. HOUSTON, W. R.: The doctor himself as a therapeutic agent, ANN. INT. MED., 1938, xvi, 1416-1425.
22. STRECKER, E. A., and EBAUGH, F. G.: Practical clinical psychiatry, 1935, P. Blakiston's Son and Co., Philadelphia, Pa., pp. 488-489.
23. CAMPBELL, J. D.: Psychiatry in general practice: an orientation, Jr. Am. Med. Assoc., 1939, cxii, 2577-2581.
24. BURLINGAME, C. C.: Hard facts about psychiatry, Jr. Am. Med. Assoc., 1939, cxiii, 377-380.

CASE REPORTS

HERNIA OF THE DIAPHRAGM; REPORT OF TWO CASES *

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ALTHOUGH an increased number of cases of hernia of the diaphragm is being recorded, it may be still regarded as a rare condition. A great number of types and varieties and degrees of hernia have been recognized and various attempts at classification have been made, based on anatomy, embryology, etiology, and contents, but it is impossible to distinguish these clinically. Perhaps the most satisfactory method is to consider these all as (1) traumatic or (2) non-traumatic. The traumatic may be divided into (A) indirect, injury resulting from a crushing blow to the chest or abdomen; (B) direct, the result of the formation of a window of the diaphragm following stabbing or shooting. The non-traumatic may be (a) congenital deficiency or (b) acquired after birth.

Hedblom¹ in 1932 mentioned between 1400 and 1500 reported cases of various types and added 600 from his own records. Since then, Stobie² has reported five cases, Marks,³ 29 cases, Harrington and Kirklin⁴ from the Mayo Clinic, 241 cases including 131 operated upon between 1900 and 1937. Root and Pritchett⁵ reported 31 cases from the Cleveland Clinic and Trusdale⁶ reported 303 cases in children including 13 of his own operative cases. More recently, Bowen⁷ has given a good summary of the recent literature and has summarized the facts regarding incidence, symptoms, physical signs, diagnosis, prognosis, classification, treatment, and technic of operation, largely based on the above mentioned reports. These phases are too lengthy to discuss in this paper.

There is considerable variety in the reported frequency of this condition. At the Mayo Clinic, it is estimated that diaphragmatic hernia occurred once in about every 18,000 roentgen-ray examinations. Only two cases were found in the Guys Hospital in London from 1856-1920, and MacMillan reported three cases in 15,000 examinations in the United States General Hospital No. 8. In the Waterbury Hospital,⁸ only six cases have been recognized in the past six years out of about 24,000 roentgen-ray examinations, about one a year or one every 4,000 cases.

To some extent this variation is due to the definition of what is considered true hernia. Some do not include the minor forms of esophageal shortening and hiatus hernia.

The following two cases have seemed to be sufficiently unusual and interesting to be worth recording in detail, especially as it was possible to secure an artistic record of the first case.

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From the Medical Service of The Waterbury Hospital.

CASE 1

Mrs. L. C. S. was 54 years of age when she first consulted me in 1931 complaining of headaches and of some nervous troubles. She gave a history of having had typhoid fever, "typhoid pneumonia," and the exanthemata as a child, and curvature of the spine since childhood. She had a fracture of the right hip at the age of 42 and pneumonia at 52.

In 1923, following a series of attacks of upper abdominal pain off and on for five or six years, which had been relieved only by morphine hypodermically, she had a cholecystectomy and appendectomy. She apparently developed bronchopneumonia postoperatively. Notes from the hospital record give no details of the operative findings. The pathological report, however, showed a chronic, fibrotic, obliterative appendicitis and a gall-bladder measuring 6.5 cm. in length which grossly and microscopically showed no evidence of inflammation.

She had had frequent severe headaches which she felt were related to her digestion, or her "liver," occurring at 4 or 5 o'clock in the morning, and not related to eyestrain. She had frequent colds with sore throats and had considerable mucus in her throat but no actual tonsillitis. There was no allergic history. In her cardio-respiratory past history she had complained of moderate dyspnea on exertion for years. She had a chronic cough and was very susceptible to bronchial colds. She had occasional edema of her ankles.

She had a fair appetite but was a small eater. She was troubled with gas and some gulping or regurgitation of food after meals, and at times had a feeling of constriction and of fullness in the abdomen. Her bowels moved regularly although she occasionally took "liver pills" for gas. She had nocturia once or twice most of the time, occasionally some frequency and dysuria with her colds. Her menses began at 12 and were apparently normal. She was married at the age of 30 but was never pregnant. Menopause occurred at 45.

She had been stoop-shouldered from a curvature of the spine since childhood, but no further details were known. Her weight stayed around 110 to 115 pounds.

Physical examination showed a rather remarkably deformed, slightly-built adult woman with an upper dorsal kyphosis and left lateral scoliosis resulting in her left shoulder being higher than the right, and constricting her chest laterally. This brought her costal margin almost to the iliac crest. She was quite agile, cheerful, friendly and coöperative. Her eyes, ears, and nose were normal; her tonsils were enlarged and boggy. Her soft palate and uvula were swollen most of the time. Examination of her chest was unsatisfactory because of the deformity and asymmetry. Her heart seemed moderately displaced to the right but the sounds were normal. Her blood pressure ranged from 165 mm. Hg systolic and 95 diastolic and 170 systolic and 110 diastolic to 120 systolic and 95 diastolic at various times. There was very little expansion of her chest wall and with the rigidity and curvature of the spine, the distant breath sounds on the left were not thought abnormal, as there seemed to be no definite dullness on percussion. She almost constantly showed fairly numerous, moist râles in her right upper chest, front and back, with occasional pleural friction sounds. Her abdomen was much shortened, the liver was enlarged but with her deformity that did not seem particularly abnormal.

In 1934, she was sick for about four weeks with bronchopneumonia, following which she complained of pains in her abdomen with some regurgitation of food after eating. A mass of about 8 by 10 cm. was found in her left mid-abdomen which did not seem to be connected to the pelvic organs or related to her renal or intestinal tract. She was admitted to the Waterbury Hospital March 5, 1934 for observation and gastrointestinal study with question of intestinal obstruction. Her temperature, pulse and respiration were normal. Hemoglobin was 98 per cent; erythrocytes 4,700,000; leukocytes 5,000; polymorphonuclears 64 per cent; monocytes 8; lympho-

cytes 26; endothelials 2; blood Wassermann test was negative. The gastrointestinal roentgen-ray report of March 5, 1934, was as follows:

The fluoroscopic examination showed gross pathologic findings in the left chest. The barium solution passed down the esophagus to the usual position at the cardiac end of the stomach. (Figures 1, 2, and 3.) From this point, it passed directly up-

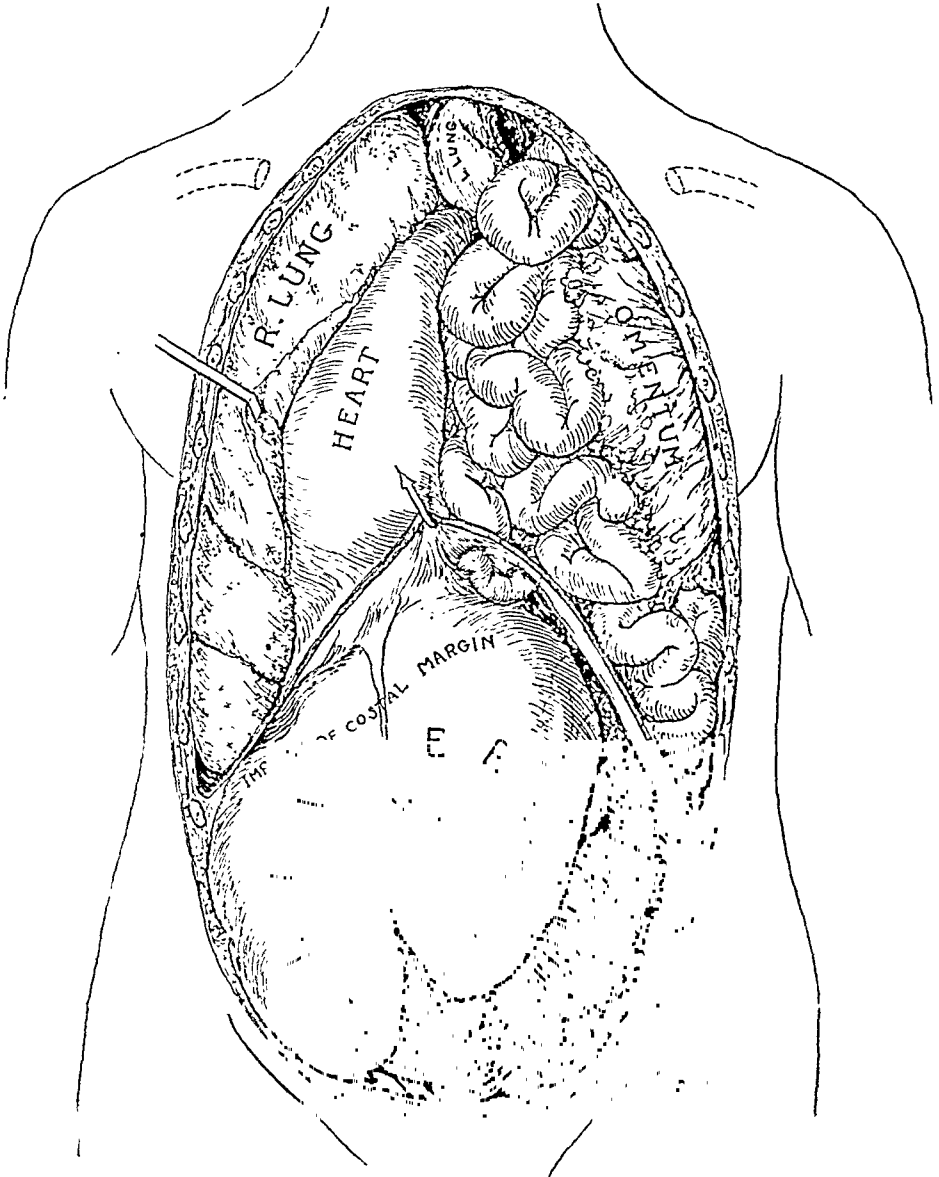


FIG. 1.

ward to within two inches of the clavicle, then forward and downward. The duodenal cap was seen only in lateral view. A gas bubble was in the stomach, within 1 cm. of the level of the clavicle. Above this was a tissue shadow which was probably part of the diaphragm. There was a small amount of barium in the stomach at the end of six hours and a large amount of barium in the small intestines, lying in the left chest. The head of the meal had reached the cecum which lay in the midline of

the pelvis. At 24 hours, about half of the barium was evacuated. No roentgen-ray connection could be made out of involvement of the mass in the abdomen with the small or large intestines.

Diagnosis: Eventration left half of diaphragm.

She was seen by two of the surgical staff in consultation at the time. It was agreed that she was a poor surgical risk and that the abdominal mass was probably

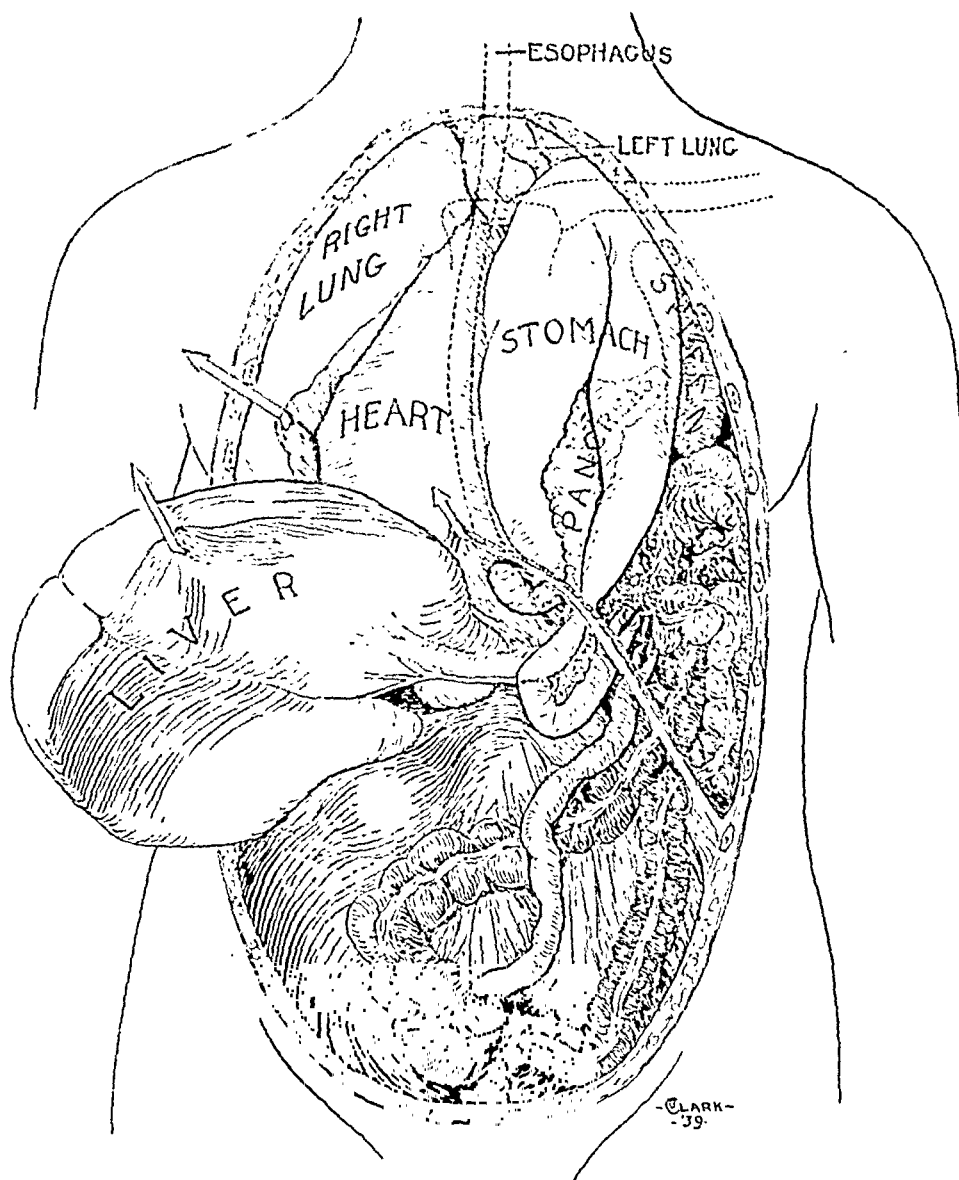


FIG. 2.

a cyst of the mesentery. With a bland diet and small doses of barbiturates her symptoms subsided. She was seen off and on during the subsequent three years for a variety of minor complaints, but in general, her health was not as good as in previous years. She had increasing dyspnea on exertion, edema of her ankles, and some cystitis and pyelitis. Her vision was disturbed by some vitreous opacities. The mass in her abdomen seemed to be getting larger. In 1937, after an episode of

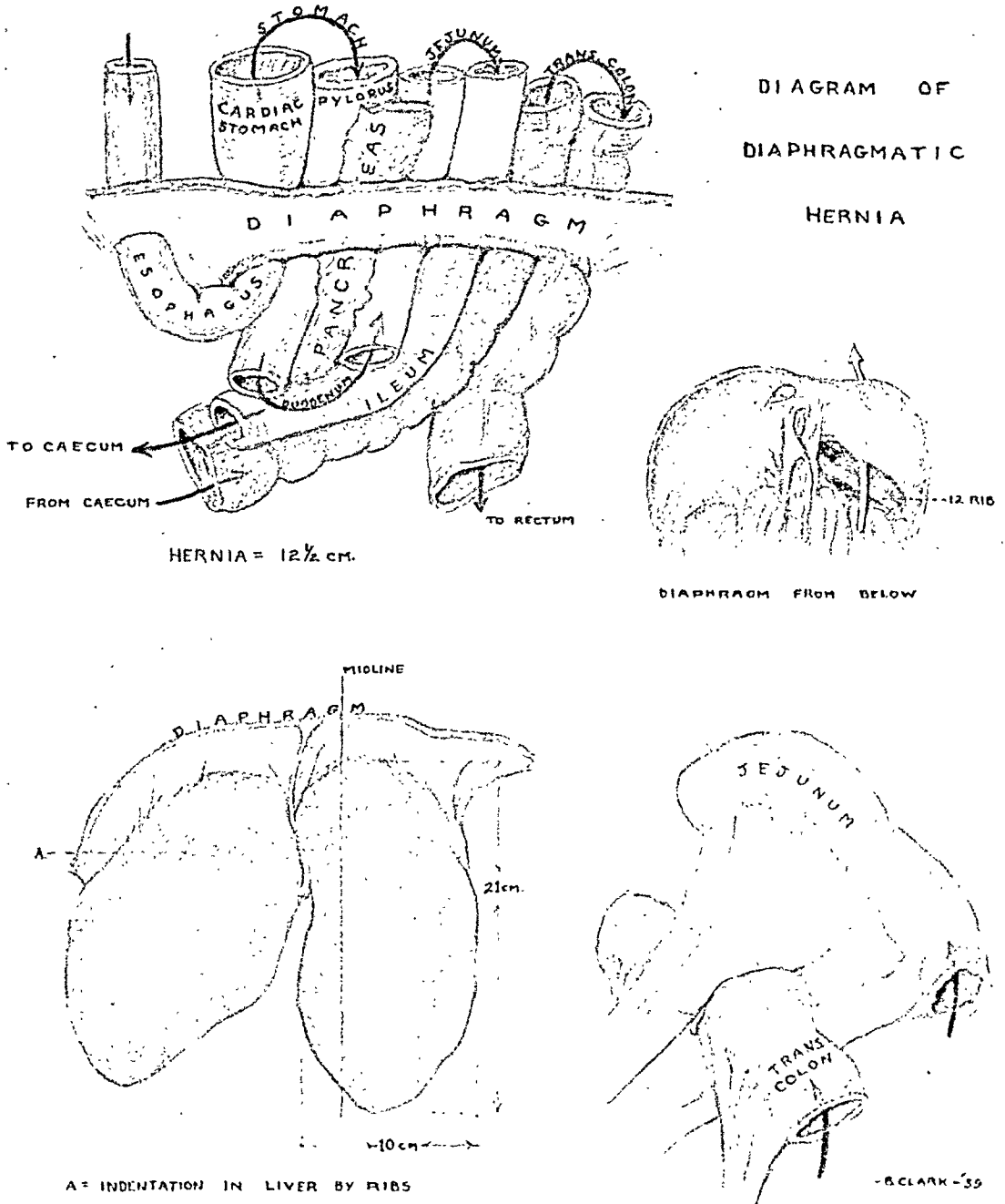


FIG. 3.

cystitis, a pyelogram (figure 4) was taken which showed the kidneys, ureters and bladder to be normal and to have no connection with the abdominal tumor. She seemed to improve after that, and was quite active. She took several long automobile trips in the summer of 1937 and spent several weeks in Florida the following winter. During October and November, 1938, she had more severe headaches, was

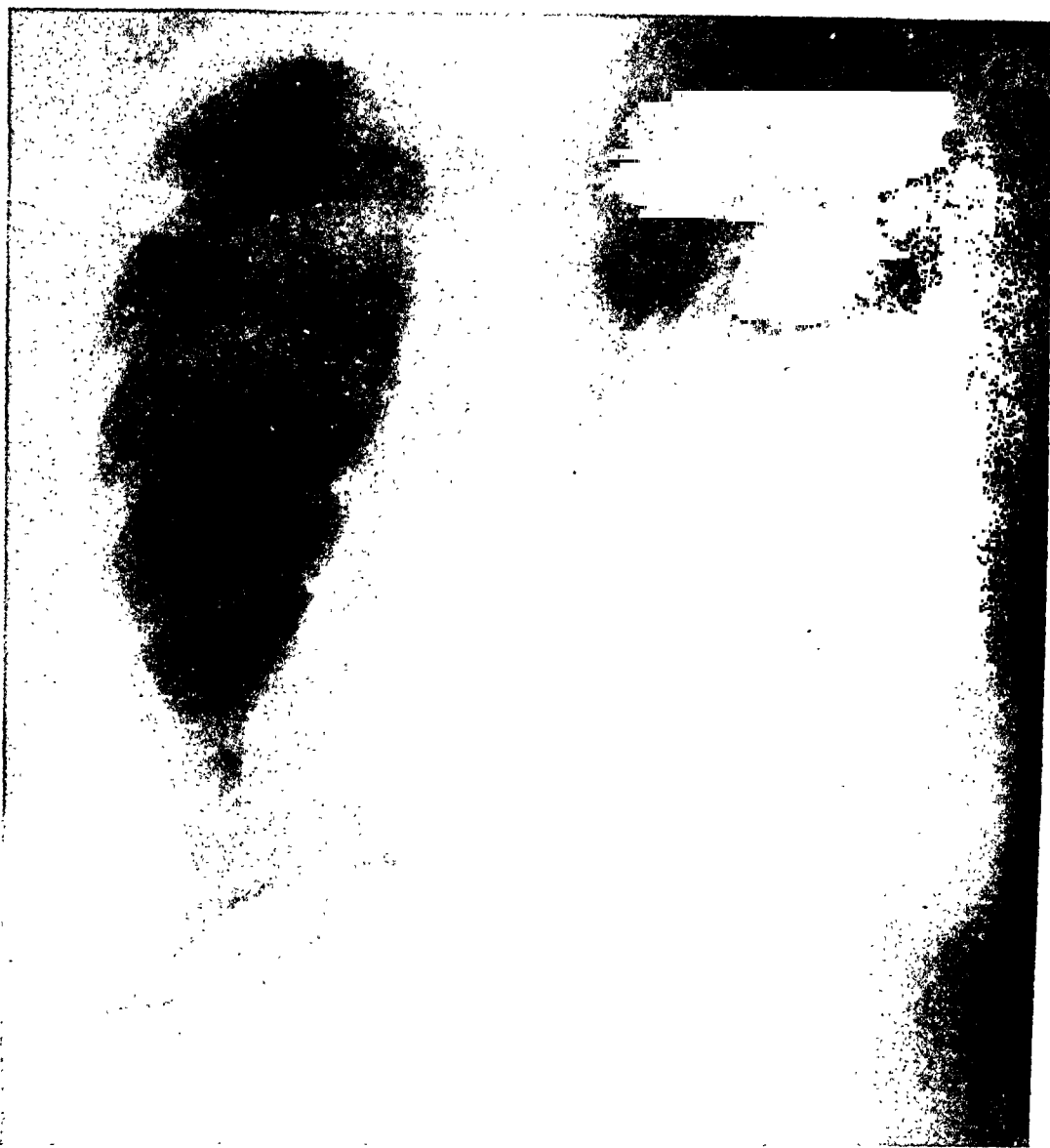


FIG. 4. Chest roentgen-ray showing barium meal in the stomach within the left thorax. The gas bubble is almost on the level of the clavicle.

weaker and more dyspneic. The week before Christmas, she developed a cold and a deep cough. She became much weaker, and died suddenly in her sleep Christmas afternoon, apparently a cardiac death.

Permission for an autopsy was granted and performed through the courtesy of the undertaker about 18 hours after death and after embalming, with the findings as follows:

The body was that of a white adult female apparently about 60 years of age. The body was well-developed and well-nourished; the head and neck were not remarkable. The thorax was deformed by a posterior curvature of the thoracic vertebrae with some left lateral scoliosis. There was a lateral compression of the thorax which greatly increased the anterior and posterior diameter of her chest. The costal margin reached nearly to the iliac crest. There was a mid-line operative scar from the umbilicus to the symphysis.

The body was opened by mid-line incision and the breast plate removed to expose the thorax. A remarkable picture (figure 1) was presented. The left thoracic cavity appeared entirely filled with coils of small intestines, all lying above the diaphragm. No lung was visible on the left side. The pericardial sac was suspended about perpendicularly, lying to the right of the mid-line. The right lung was compressed by the pericardium. Below the diaphragm, the entire abdominal cavity was filled by the liver which was flattened and bilobed, extending to within two inches of the symphysis pubis. The mass felt during life was the large left lobe of the liver. The heart was about normal in size. There were no pericardial adhesions. The valves and endocardium were smooth and glistening and normal in appearance. The coronary arteries seemed normal and there was no special sclerosis.

The left lung was not visible on inspection but was found lying high up in the left apex, almost completely hypoplastic, not over six or seven cm. in any dimension, white in color. There was very little anthracosis. The cut section was spongy and normal in appearance. The right lung was dark in color and was completely adherent to the thoracic wall throughout. There was considerable anthracosis but no gross scarring. The cut section showed congestion at the base. The diaphragm seemed normal on the right, but on the left there was an opening along the posterior half, 12 to 13 cm. in length and about 2 to 3 cm. in width. The margin of the opening was smooth, hard, and rounded, and the cut section showed a well-developed muscle band with fibrosis. The anterior half of the left diaphragm was normal.

The esophagus was lying in the posterior mediastinum and passed normally through the diaphragm. (Figure 2.) At a point about two cm. to the left, the cardiac end of the stomach appeared through the hernia. It passed upward and backward to the level of the clavicle where at its greater curvature, it passed forward and downward, about normal in size and shape, to the pylorus which joined the duodenum just above the level of the diaphragm. The stomach was full of partially digested chyme. The duodenum could be traced downward through the opening in the diaphragm. The ampulla of Vater was located and the bile duct found passing up to the hilus of the liver. The jejunum then passed upward and was lying in the anterior left thoracic cavity. The ileum was traced back downward through the hernia. The terminal 18 inches passed downward across the posterior abdominal wall under the liver to the right iliac fossa where it joined the cecum in its normal position. The appendix was not found. The cecum was dilated but otherwise was normal. The ascending colon passed upward, parallel to the ileum through the opening in the diaphragm. The transverse colon was found lying within the left thorax. The omentum was also all above the diaphragm, lying against the left axillary wall. The descending colon passed downward along the left posterior abdominal wall directly to the rectum.

The pancreas was lying partly in the hernia, parallel to the stomach in about the center of the thorax. It appeared normal and was of the usual consistency.

The spleen was larger than normal, about 15 by 6.5 cm. It was dark and congested and was lying in the left posterior upper thorax, almost under the scapula. It had the appearance of chronic passive congestion.

The liver was deformed, flattened by the pressure of the costal margin against the lumbar lordosis into two lobes of about equal size, appearing as a pair of saddle bags, occupying the whole abdominal area. Each lobe was about 10 cm. wide by about 20 cm. in length and from 3 to 5 cm. in thickness. The cut surface appeared normal except for heavy strands of fibrosis through the hilum. A small quadrate lobe was present; the gall-bladder was absent.

The kidneys were in the usual position. They were smaller than average, the right measuring 10.5 by 6.5 cm., the left, 9.5 by 4.5 cm. They were rather lobulated. The uterus was atrophic. Small, hard glands were present in the pelvis but otherwise

no abnormal structures were noted. The spine was shaped like a question mark or shepherd's crook but did not appear grossly abnormal except in the region of the lower lumbar vertebrae where it seemed to be thickened. The spine seemed absolutely rigid. Sections were taken from the different organs but microscopic examination was essentially negative, except for some generalized arteriosclerosis and congestion of the right lung. Diagnosis was:

1. Arteriosclerotic heart disease
2. Bronchopneumonia
3. Hernia of the diaphragm (congenital)
4. Kyphosis and scoliosis of the spine.

DISCUSSION

The deformity of her skeletal structure from childhood, the almost complete transference of her abdominal viscera into the left thorax without any history of acute symptoms, the under-developed condition of her left lung, and the fibrous margin of the diaphragm all point to a congenital etiology of her condition. It is of interest that with such an abnormal arrangement of her organs, she survived (1) typhoid fever as a child; (2) bronchopneumonia at least three times during her life; (3) a fracture of her hip at 40; (4) a cholecystectomy and appendectomy at 45, and lived to be nearly 60 years of age. Although never very robust, she thoroughly enjoyed life.

The surgeon at the time of her operation did not suspect anything abnormal in the position of her organs, the gall-bladder and the appendix being in about the expected positions. From the pathological report of the gall-bladder and appendix, it is possible that the symptoms she had had at that time may have been related to the hernia. However, she apparently had fewer attacks after the operation. There evidently had been considerable enlargement of the liver during recent years.

Although the roentgen-ray diagnosis was that of eventration of the diaphragm, the actual condition was hernia. Eventration is that condition in which one leaf of the diaphragm is weakened or paralyzed and is pushed upward, very much thinned, compressing the lung, but always keeping the abdominal and thoracic viscera separated. Hernia, as in this case, is a condition where an opening in the diaphragm permits the abdominal contents to be extruded into the thorax within the pleural cavity and in direct contact with the mediastinum and lung.

CASE 2

Another case of almost equal interest and presenting some unusual problems of diagnosis and therapy was a 15 year old Italian boy who was brought into the Waterbury Hospital by ambulance, February 11, 1937. The story obtained from the attending physician was that the boy had returned from school the day before, complaining of a pain in the abdomen. In spite of this, he ate a large supper. Later in the evening, he began to vomit and this continued throughout the night. The boy was given pantopon grains $\frac{1}{2}$ about 9 p.m., at which time physical examination seemed to be negative. At 8:30 in the morning, the visiting nurse gave him two enemas which returned clear. The temperature was 99.8° F. The doctor saw him again at 3:30 p.m. and immediately sent him to the hospital by ambulance.

At the time of admission, the boy was extremely cyanotic, dyspneic, and complained of severe pain in the upper right chest. He was gasping for breath, respirations were 46, pulse was 120, and temperature was 103°. Blood pressure could not be



FIG. 5. Chest roentgen-ray six hours after the barium meal which is still mostly in the thorax.

determined. Hasty examination of the chest revealed what was thought to be complete consolidation of the whole left lung and the lower right chest. While being examined, the boy went into convulsions and died, 25 minutes after admission.

Portable roentgen-ray of the chest which was taken on admission to the hospital was rather unsatisfactory. It showed the right costophrenic angle in its usual position and the heart displaced out of the left chest. An area of pneumothorax, approximately 10 cm. in diameter, was seen in the upper part of the left chest. Below this was a mottling suggestive of fecal material. The patient died before the examination could be repeated. Diagnosis was left pneumothorax.

The leukocyte count showed 24,300 per cm., 87 per cent neutrophils, 7 small lymphocytes, 1 large lymphocyte, and 5 mononuclears.



FIG. 6. Abdominal film taken six hours after barium meal with the head of the meal in the ascending colon, also showing the old fracture of the neck of the right femur.

The autopsy, performed 20 hours post mortem and after embalming, showed well-developed and nourished young adult male, with no abnormal external features. A mid-line incision was made and the breast plate removed to expose the thorax. The stomach and part of the transverse colon were found resting in the left pleural space. The left thorax also contained considerable quantities of gas under pressure and a small amount of greenish fluid in which undigested food particles were found.

The heart was essentially normal, except for marked displacement to the right. The left lung was decidedly underdeveloped. The lobes were quite small. The apical portion of the upper lobe was fully expanded and appeared normal but the lower



FIG. 7. Pyelogram showing the left renal pelvis and ureter, also the spinal scoliosis.

portion of the upper lobe was collapsed. Most of the lower lobe was also collapsed and completely devoid of air. The right lung showed partial atelectasis. There was no evidence of pneumonia in either lung.

The lower mediastinum was partly digested on the left, as a result of the action of gastric juice.

The esophagus and the right diaphragm were normal. The left diaphragm was deficient in its postero-lateral aspect, leaving a window large enough to admit a man's fist. The edges of the opening were perfectly smooth and slightly thicker than the adjacent normal diaphragm. The appearance was that of a congenital deficiency of the diaphragm.

The bulk of the stomach and part of the transverse colon were found in the left

thoracic cavity. A small amount of the pyloric end of the stomach was found below the diaphragm. The stomach contained about a quart of undigested foodstuff. On the lesser curvature of the stomach, about 3 cm. from the esophageal opening, was found a perforation which allowed the stomach contents to escape into the left pleural space. There was some question as to whether the perforation was ante mortem or post mortem, but the microscopic examination showed the perforation to have occurred before death. A portion of the transverse colon was found in the left thorax, otherwise the gastrointestinal tract was entirely normal. The liver and kidneys were negative. The spleen showed acute splenic tumor. Final diagnosis:

1. Diaphragmatic hernia
2. Gastric ulcer with perforation into the thorax
3. Rudimentary left lung
4. Atelectasis
5. Pneumo-hydro-thorax, left (gastric contents)

COMMENTS

From the appearance of the diaphragmatic opening, this patient undoubtedly also had a congenital hernia of the diaphragm. The sudden onset of his symptoms was apparently due to the perforation of his ulcer. If he had been sent to the hospital immediately after the onset of his pain, and if proper roentgen-ray study could have been made promptly, it is possible that the condition could have been recognized. Whether a surgical intervention could have been successful can only be a matter for speculation. An approach through the lateral thoracic wall might have exposed the ulcer and permitted repair.

DISCUSSION

The above cases are examples of how nature can adapt body function to extreme congenital deficiencies of structure and also what complications may develop to confuse the physician. They also demonstrate a few of the possible combinations of symptoms which may occur in diaphragmatic hernia. It is only necessary to reemphasize the statements made by others that the diagnosis can usually be made by roentgen-ray examination, but the possibility of this condition must first be considered as in many cases the symptoms may simulate cardiac, pulmonary, gastric, gall-bladder or intestinal disease.

SUMMARY

1. True hernia of the diaphragm is a rare condition as shown by the infrequency of its recognition in many clinics.
2. Two cases of congenital hernia of the diaphragm with unusual symptoms and complications have been reported.
3. Symptoms of diaphragmatic hernia may simulate cardiac, pulmonary, gastric, gall-bladder and intestinal disease and should be considered in the differential diagnosis of many diseases.

BIBLIOGRAPHY

1. HEDBLUM, CARL A.: Hernia of the diaphragm, *Cycl. of Med.*, 1932, iv, 553.
2. STOBIE, GEO. H.: Diaphragmatic hernia (a review of recent literature and report of five cases), *Canad. Med. Assoc. Jr.*, 1937, xxxvi, 136.
3. MARKS, J. H.: Diaphragmatic hernia and associated conditions, *Am. Jr. Roentgenol.*, 1937, xxxvii, 613.

4. HARRINGTON, STUART W., and KIRKLIN, B. R.: The clinical and roentgenological manifestation and surgical treatment of diaphragmatic hernia, with a review of 131 cases, *Radiology*, 1938, xxx, 147.
5. ROOT, JOSEPH C., and PRITCHETT, CLARK P.: Diaphragmatic hernia, *Cleveland Clin. Quart.*, 1938, v, 203.
6. TRUSDALE, P. E.: Diaphragmatic hernia in children with a report of 13 cases, *New Eng. Jr. Med.*, 1935, ccxiii, 459.
7. BOWEN, ARTHUR: Diaphragmatic hernia; review of literature, *Am. Jr. Surg.*, 1938, xxxix, 4.
8. Personal communication, Dr. J. L. Harvey, Roentgenologist, Waterbury Hospital.

SPONTANEOUS HEMORRHAGE INTO THE SUPRARENALS (SUPRARENAL APOPLEXY) *

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HEMORRHAGE into the suprarenals is a rare occurrence which usually results fatally and is difficult to recognize. The diagnosis is rarely made until after autopsy. Suprarenal hemorrhages have been more frequently observed in the newborn and in young children. The degree of hemorrhage varies from small petechial areas in the suprarenal glands to massive hemorrhages with extensive destruction of suprarenal tissue. These conditions have been described in the literature as acute hemorrhagic adrenalitis, Waterhouse-Friderichsen syndrome, spontaneous suprarenal hemorrhage and suprarenal apoplexy.

The cause and origin of the hemorrhage into the suprarenals are not definitely known. In considering the etiology, one must first differentiate between suprarenal hemorrhages in the newborn and those which occur in older children and adults. In the newborn, trauma and asphyxiation in prolonged labor are contributory factors, according to some observers. Prolonged and difficult deliveries may easily lead to circulatory stasis in the infantile abdominal organs. The mechanical effect of Schultze's resuscitation method for the newborn has been mentioned as a possible cause. There is some relationship between eclampsia in the mother and vascular lesions of the suprarenals in the newborn according to other authors.¹ In hereditary syphilis of the newborn the suprarenals have been found to contain more or less extensive hemorrhagic areas.²

In older children and adults suprarenal hemorrhages have been found in the course of acute infectious diseases, especially scarlet fever, diphtheria, meningococcus meningitis and pneumonia.^{3, 4} Alcoholism, syphilis, and hemophilia have also been associated with some cases.

Up to the present time there are two predominating theories which attempt to explain the origin of hemorrhages into the suprarenals. One view lays stress upon the suprarenal vascular system; the other considers some lesion of the glandular parenchymia to be the primary cause. The evidence appears to be more convincing in support of some disturbance of the suprarenal circulatory system, which may be derived from a condition either of vascular traumatism, venous thrombosis, or bacterial emboli in the capillaries of the gland. In hitherto

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Report of case in an adult: From the Medical Service of the Sternberg General Hospital, U. S. Army, Manila, Philippines.

published cases of suprarenal apoplexy, venous thrombosis in the suprarenal glands has been definitely established.^{1, 5} Whether this venous thrombosis, a sign of circulatory disturbances in the gland, is the cause of the hemorrhages, or whether the hemorrhage is due to a lesion of the suprarenal cells and the thrombosis represents only a result of the disturbances in the parenchymal congestion, is questionable. Few authors consider the primary injury to the organ as the essential cause of suprarenal hemorrhage in older children and adults.

Anatomically, the vessels of the suprarenal glands are characterized by extraordinary fineness of their walls and intimate contact with the cells. This may account for the greater frequency of suprarenal hemorrhages in the newborn as a result of venous congestion in the course of difficult, prolonged labor.

The clinical manifestations of hemorrhage into the suprarenal glands depend upon the degree of hemorrhage and the resultant destruction of suprarenal tissue. Since all the cases reported are those that have resulted in death, and have come to autopsy, most of our knowledge is confined to extensive hemorrhages of the suprarenals.

The signs and symptoms of spontaneous hemorrhage into the suprarenal, or suprarenal apoplexy, are those of sudden, total suprarenal insufficiency, characterized by circulatory collapse. Associated with this, there is usually a characteristic generalized purpuric eruption of the skin. The onset is sudden and alarming, and death ensues rapidly, usually within 24 hours. The patient appears to be in shock; the blood pressure is low and sometimes not obtainable; the pulse is small and rapid, respirations are increased, and the extremities are cold. There is marked pallor at the beginning of this condition, but later this is replaced by cyanosis which finally resembles postmortem lividity, especially over the back and hips. Severe gastrointestinal disturbances, with nausea, vomiting, and abdominal pains are present.^{6, 7, 8} The temperature rises rapidly to a high level,⁹ and drops immediately before death. The patient remains mentally clear. The picture is not unlike that seen in the splanchnic shock of acute hemorrhagic pancreatitis.¹⁰

The purpuric eruption of the skin found in most reported cases of suprarenal hemorrhage, especially in older children and adults, is most characteristic. It may resemble a purpura hemorrhagica, which in children is considered as the most probable diagnosis before blood studies are made. This purpuric eruption is reported with remarkable consistency in suprarenal hemorrhages that have ended in death. Even as early as 1904, Langmead,¹¹ in the *Lancet*, reported three cases of suprarenal hemorrhage in older children, each of whom had a purpuric or petechial eruption over the entire body. In two cases reported by Rabinowitz¹² in 1923, each child had this generalized eruption. Herrick observed this same eruption in the cases of massive adrenal hemorrhage associated with meningococcus meningitis in Army service during World War I. These purpuric spots appear shortly after the onset, and are first seen on the trunk and the extremities. The petechiae are bluish-red to purple in color, and increase in size. They may be found on the palms of the hands and the soles of the feet. About the smaller joints, and especially the hands, these petechial spots appear to coalesce. The entire body may be covered with this eruption; and it persists for several hours after death. There is no serum beneath the spots. Associated with the eruption there is usually a postmortem lividity of the skin, especially in the dependent regions.

The blood findings have not been uniform enough to support any conclusions, although there is a tendency to high leukocytosis.¹³

Treatment in these cases has been directed towards combating the sudden collapse of the circulation due to sudden adrenal insufficiency. The administration of 10 per cent dextrose in physiologic solution of sodium chloride intravenously is indicated. The addition of a few minims of a 1:1000 solution of adrenalin may be used. Certainly, if the diagnosis of adrenal insufficiency is made, the administration of extract of adrenal cortex is warranted.¹⁴

Herewith is reported a case of bilateral spontaneous hemorrhage into the suprarenals of an adult:

C. A. K., a 43 year old white male, unmarried, was admitted to Sternberg General Hospital, Manila, P. I., on December 26, 1937, at 5:00 p.m. complaining of gastrointestinal distress and weakness in the lower extremities.

Personal History. He had been a soldier for the past 11 years. Previous to that time he had worked on farms. He had served a tour of duty in the Philippines in 1929, had returned to the States, and at the time was serving a second tour in the Philippines. In 1927 he had contracted syphilis, for which he was under treatment for six years. He stated he had become seronegative. In 1929 he had been treated for bubo and also for "stomach trouble."

To his knowledge there were no familial diseases.

The patient was a steady drinker and frequently went on an alcoholic debauch. Such episodes lasted about two to three days, during which time he drank a quart of whiskey daily.

History of Present Illness. The patient was alert and oriented. He stated that he was getting over a mild drinking spree when, shortly before admission, he felt very weak and had pain in the abdomen associated with nausea. Shortly after admission he complained of pain, particularly in the epigastrium, and vomited several times; this vomitus was green. The temperature was 100° F. on admission. He continued to complain of abdominal distress, and in two hours the temperature went to 104.2° F. Later he complained of pain in the hips.

At 4:00 a.m., 11 hours after admission, the patient was seized with severe cramp-like pain in the abdomen, and the examining physician at that time noticed purpuric eruptions on the abdomen and extremities. They were widely scattered. There was no spasm or rigidity of the abdominal muscles.

At 7:00 a.m. the patient suddenly became alarmingly worse. On inspection he seemed in shock. The pulse could not be felt at either wrist. The lips were blue. No blood pressure could be obtained on several attempts. The entire trunk and body, including the upper and lower extremities, were covered with a petechial eruption ranging from dark blue to black in color. Adrenalin was given; later digitalis preparations were used, and heat was applied to the entire body. The heart tones were distant; no murmurs were heard; the rhythm was regular. The lungs filled with moist crepitant râles throughout both sides; respirations were increased in rate but not labored. The abdomen was soft. The liver and spleen could not be palpated. The pupils were equal and reacted to light; there were coarse tremors of the hands. The patient was given 10 per cent dextrose in physiological solution of sodium chloride intravenously at once; he appeared to regain some color after this was given. The blood pressure now obtained was 76 mm. Hg systolic and 60 mm. diastolic. The heart tones were still weak.

The dependent portions of the body, particularly the back and buttocks, were assuming a postmortem lividity. The petechial eruption seemed more intense. The patient was rapidly sinking to the original state of collapse. He was mentally clear. The temperature dropped from 106° F. to subnormal shortly before 11:00 a.m. The

extremities were rapidly becoming cyanotic. At 11:00 a.m., while conversing with his physician the patient suddenly died.

<i>Laboratory Findings</i>	: Red blood cells 3,290,000.
	: White blood cells 37,850.
Differential	: 91% polymorphonuclears.
	: 6% lymphocytes.
	: 3% monocytes.
Platelets	: 200,000.
Coagulation time	: 3 minutes.
Bleeding time	: 2¼ minutes.
Icterus index	: 8
van den Bergh	: Delayed direct reaction.
Blood culture	: Negative.

Urine was positive for albumin, and coarse granular casts were found.

Diagnosis. 1. Circulatory collapse of unknown cause. 2. Purpura hemorrhagica, non-thrombocytopenic type.

Autopsy. The autopsy was performed three hours after the patient's death.

External examination: The body is that of a well developed and well nourished white American male. Postmortem rigidity is moderate. Lividity is marked, especially in dependent portions. Pupils are dilated and equal in size. Nares and external auditory canals are negative. A frothy fluid exudes from mouth. Right inguinal region shows an old healed linear scar. Entire surface of skin shows a purpuric type of rash or mottling. These areas are bluish-red, discrete, and vary in size from pin-head to one centimeter. They are present in the thick skin of the hands and feet.

Thorax: Both pleural cavities contain a small quantity of clear straw-colored fluid. No adhesions present.

Both lungs are voluminous and boggy throughout. A few superficial small red spots are present in the interlobar pleurae. On section, much frothy fluid escapes.

Heart: Pericardial sac and cavity normal. Right auricle and ventricle contracted and of moderate thickness. Cardiac muscles pale, red, and moderately firm. Coronary arteries patent.

Abdomen: Stomach dilated, small and large intestines are markedly contracted. No free fluid present. Appendix normal. Liver moderately enlarged. Surface smooth and pale yellow, mottled with brighter red intermingled tissue. On section, tissue appears as surface. Gall-bladder is thin walled, distended and filled with thin bile. Common duct patent. Spleen moderately increased in size, and soft. Kidneys normal size and dark red. Capsule easily removed. Surface capillaries distinct. On section, moderate congestion present. Pancreas normal in appearance.

Suprarenals: Left suprarenal is enlarged and enclosed in a large mass of fatty tissue. On section, medullary portion shows a hemorrhage which has practically destroyed it and infiltrated into the cortex. Right adrenal is small, dark red, and firm. On section, there is a diffuse hemorrhage throughout.

Gastrointestinal tract: Stomach is dilated and filled with greenish gray fluid material. Mucosa slightly congested. Intestines contracted and contain very little greenish mucoid material. A few areas of slight congestion present. No hemorrhages found in either stomach or intestines.

Bladder negative.

Scalp and skull normal. Brain: Slight congestion found.

Pathological Findings:

1. Hemorrhage, spontaneous, suprarenals, bilateral.
2. Edema of lungs.
3. Fatty infiltration of liver with acute congestion.
4. Congestion, acute, of kidneys.

Histological:

Suprarenal: The capsule shows a very slight degree of irregular thickening. The normal architecture of the tissue is obliterated greatly by the presence of massive hemorrhage. The zona glomerulosa is not distinct and clear cut. Only small collections of cells are robust and contain an abundant amount of lipoid substance. The zona reticularis is not distinct, because of the marked hemorrhage. However, the cellular pigment stands out prominently. Only a small amount of medulla is noted in the sections, and here the cellular picture is indistinct because of the marked hemorrhage. No tumor or inflammatory exudate noted. The large vessels present in the outer hemorrhagic fat tissue are thick walled, showing prominent intimal and medial thickening.

Spleen: Capsule thickened. Congestion is prominent. Occasional irregular areas of hemorrhage are noted. Cellular proliferation is prominent. Trabeculae are thick and prominent. The malpighian corpuscles are not remarkable. The central arterioles are thickened and show intimal hyalinization.

Liver: The parenchyma shows marked diffuse fatty metamorphosis. The central veins are dilated and engorged. There is prominent central capillary congestion. The portal vessels are dilated and engorged. There is no significant portal cellular reaction.

Pancreas: Not remarkable, except for slight fatty infiltration.

Kidney: Congestion is marked. The normal architecture of the glomeruli is obscured by the marked congestion. The tubular epithelium is not remarkable. There are no significant arteriosclerotic changes noted, nor is there any cellular inflammatory exudate present.

Brain: The meningeal vessels are dilated and engorged. No exudate noted. The parenchyma is not remarkable except for prominent capillary engorgement.

Histological Diagnosis:

Suprarenal : Hemorrhage, massive.

Spleen : Hyperplasia, acute toxic (acute splenic tumor).

: Congestion marked.

: Hemorrhage.

Liver : Fatty metamorphosis, severe. Congestion.

Brain : Congestion, meningeal, and parenchymal.

SUMMARY AND CONCLUSIONS

Spontaneous hemorrhage into the suprarenals is a rare condition, characterized by sudden onset of circulatory collapse associated with generalized purpuric eruption, and resulting in rapid death. Diagnosis is rarely made before death. The cause and origin of suprarenal hemorrhage are not definitely known. The condition must be differentiated from that occurring in newborn infants and that found in older children and adults. Venous congestion in prolonged difficult labors, hereditary syphilis, and eclampsia are the most frequent factors associated with suprarenal hemorrhage in the newborn. Acute infectious diseases, i.e., scarlet fever, diphtheria, meningitis, pneumonia, and disturbances of the circulatory system of the suprarenals are the more common conditions associated with suprarenal hemorrhage in older children and adults. Syphilis and alcoholism may play some part.

Thrombosis of the suprarenal vascular system, and injury to the parenchymal cells are the most frequent findings on histological examination. Acute suprarenal insufficiency results from the sudden disturbance of the glands, which, in turn, is in part the cause of the circulatory collapse. Circulatory collapse with

low or unobtainable blood pressure; rapid, small pulse; cold extremities and a generalized petechial eruption of the skin should make one suspicious of suprarenal insufficiency. Early recognition, with the administration of saline with 10 per cent glucose, and the use of extract of the suprarenal cortex seem to be the only hope in treatment of hemorrhage into the suprarenals at present.

Acknowledgment is gratefully made to H. R. Livesay, Lieut. Col., Medical Corps, U. S. Army, for the necropsy report and to J. E. Ash, Lieut. Col., Medical Corps, U. S. Army for the histological report.

BIBLIOGRAPHY

1. SCHIRADER, G.: The origin of the so-called supra-renal apoplexy, *Frankfurt. Ztschr. f. Path.*, 1939, xxxvii, 128-136.
2. QUINCHE, PIERRE: Hemorrhages from the suprarenals, *Schweiz. med. Wchnschr.*, 1930, ix, 104-108.
3. SCHNEIDAGGER, S.: Hemorrhagic infarcts of both suprarenals in septicemia, *Centralbl. f. allg. Path. u. path. Anat.*, 1933, lvii, 163.
4. SACKS, MILTON S.: Fulminating septicemia associated with purpura and bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome), *ANN. INT. MED.*, 1937, x, 1105.
5. BRUNNER, T.: Massive hemorrhage into the renal bed and apoplexy of the supra-renal body, *Deutsch. Ztschr. f. Chir.*, 1927, ccii, 248-260.
6. BRASSER, ALFRED: Contributions to the knowledge of suprarenal hemorrhages, *Klin. Wchnschr.*, 1924, iii, 738-739.
7. BARSOUM, H.: Adrenal apoplexy, *Brit. Med. Jr.*, 1936, ii, 972.
8. HASSELSTROEM, E., and HULTEN, O.: Abdominal symptoms in supra-renal hemorrhages, *Upsala Läkaref. Förh.*, 1928, xxxiv, 229.
9. PRIOR, WARFIELD, M.: Adrenal hemorrhage in children, *Southern Med. Jr.*, 1937, xxx, 306.
10. SELIGMAN, BERNARD: Suprarenal hemorrhage in the adult, *Med. Jr. and Rec.*, 1932, cxxxv, 209-213.
11. LANGMEAD, F.: Three cases of suprarenal apoplexy in children, *Lancet*, 1904, i.
12. RABINOWITZ, M. A.: Adrenal hemorrhage in infancy, *Am. Jr. Med. Sci.*, 1923, clvi, 513.
13. PEARL, FELIX, and BRUNN, HAROLD: Suprarenal apoplexy, bilateral, *Surg., Gynec. and Obst.*, 1928, xlvii, 393-400.
14. GOLDZIEHER, M. A., and GREENWALD, H. M.: Hemorrhage of the suprarenal in the newborn infant, *Am. Jr. Dis. Child.*, 1932, xxv, 324-332.

PERSIMMON PHYTOBEZOAR WITH CASE REPORT*

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PERSIMMON phytobezoar, nearly unknown in Europe, is ordinarily seen in the United States and Japan where the persimmon is native. Males, because they are more likely to eat persimmons under certain circumstances, are more frequently affected. Age seems to have no effect, cases having been reported between the ages of six and 75. Its presence is manifested within a relatively short time after ingestion of the fruit. There is, accordingly, a seasonal incidence, in the late fall and early winter, when the persimmons are ripening.

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Izumi, Isida and Iwamoto¹ defined the chemical and physical factors which combine to form the bezoar. They found that the element producing astringency in a persimmon is soluble shibuol, a phlobotannin composed of phloroglucin and gallic acid. This is present in large amounts in the unripe fruit and to a lesser degree under the fruit skin and calyx in the ripened fruit. This soluble shibuol is the cohesive material which aids in bezoar formation. The following paragraph is quoted from their report:

"One of the important properties of the soluble shibuol is that it is coagulated by the action of dilute mineral acids among others. We have proved also that the gastric juice, though weak in acidity, is capable of precipitating the soluble shibuol and coagulating it, with sufficient rapidity at body temperature. When the persimmon which still contains some soluble shibuol and accordingly is astringent in taste, is ingested unpeeled with skin, and especially when it is



FIG. 1.

taken in alone or with only a little other food into an empty stomach, as it is in most of the reported cases, then coagulation of soluble shibuol will occur in the interfragmental spaces under the influence of the gastric juice. As the coagulum of shibuol is a sticky mass, it may cement the pieces of skin into a ball."

These workers succeeded in producing an artificial phytobezoar with persimmons only, although they tried many other fruits as well.

They formed these bezoars by incubating, at body temperature, gauze sacs of macerated fruits which had been slightly acidified with dilute hydrochloric acid. The concretion was found to be formed and to be rather firm in a relatively short time after incubation started. As they had found in two cases that the bezoars contained traces of pepsin and hydrochloric acid, but no bile constituents or trypsin, they concluded that these could have been formed only in the stomach. The soluble shibuol also has the faculty of coagulating proteins and starch, thus giving additional mass to the concretion. Furthermore the shibuol had the property of inhibiting the action of the digestive enzymes, thus preventing digestion of the mass before it could be solidified. We might expect putrefaction to cause some disintegration of the mass, but this also is inhibited by the shibuol.

Pathology. The bezoar itself has a dark brown or black shiny surface. On section it is a brown rather homogeneous mass having about the color of ginger-bread (figure 1). The shape is variable, and the size between 5 and 7½ cm. in diameter.

The pathology most frequently resulting from the presence of the bezoar is a peptic ulcer, usually occurring in the prepyloric region. This ulcer may be attended by the usual complications, such as hemorrhage, perforation and peritonitis.

The indiscriminate use of purgatives may cause the passage of the bezoar, or a fragment thereof, into the duodenum causing mechanical obstruction.

Symptoms and Signs. From a review of 12 cases, including my own, it would appear that the presence of the phytobezoar produces few definite subjective or objective signs of specific diagnostic value (figure 2). Among these

Authors	Number of Cases	Symptoms + Signs													
		Nausea	Vomiting	Hematemesis	Severe Epigastric Pain	Dull Epigastric Ache	Abdominal Discomfort	Eructation	Sensation of Epigastric Lump	Peptic Ulcer Symptoms	Tarry Stools	Constipation	Diarrhea	Weight in Epigastrium	Intestinal Obstruction
Izumi et al. ¹	2														2
Copetti ²	2		2			1								1	
Allen ³	3	1	2	1	1	1		1	2	2	1		1		3
Rutledge ⁴	1									1					1
Rodgers ⁵	1	1	1		1		1					1			1
Ramstad ⁶	1	1				1				1				1	
Wyatt ⁷	1				1	1									1
McNeill	1					1	1	1		1					1
Totals	12	3	5	1	3	5	2	2	2	5	1	1	1	2	5

FIG. 2

12 cases, the following symptoms and signs and their frequency were found as follows: Palpable mass in epigastrium, 7; weight loss, 5; dull aching sensation in the epigastrium, 5; peptic ulcer symptoms and signs, 5; vomiting, 5; epigastric tenderness, 4; nausea, 3; severe abdominal pain, 3. A sensation of a lump, eructation, intestinal obstruction, vague abdominal discomfort, and a sensation of a weight in the epigastrium were each complained of twice. Hematemesis, tarry stools, constipation, diarrhea, visible peristalsis were each mentioned once.

The times and modes of onset are variable. Acute symptoms may occur within a few hours after ingestion, but usually the onset is more insidious, probably with abdominal discomfort or a sensation of weight in the epigastrium. Still later, the symptoms of the complicating ulcer may dominate the picture.

Laboratory studies of the gastric contents give no information.

The diagnosis of bezoar depends upon the roentgen-ray study of the stomach with a barium meal. On fluoroscopy, a translucent mass is seen there. Usually,

this is situated in the pyloric end of the stomach, and it frequently may be dislodged and moved about by the examiner's hand. Ulceration of the stomach wall may also be detected. The roentgenograph also shows the translucent mass, and frequently an ulcer (figure 3).

Differential Diagnosis. Phytobezoar must be differentiated from gastric carcinoma, peptic ulcer, cholecystitis and the other upper abdominal diseases. The main differential points are the finding of the translucent mass on roentgen-ray examination of the stomach, and the history of the ingestion of persimmons.



FIG. 3.

Treatment. Treatment, of course, is surgical removal. To expedite healing, an ulcer, if present, should probably also be excised.

No effort should be made to remove the bezoar by the use of purgatives, as such a procedure might cause the bezoar to pass into the intestine and cause obstruction.

CASE REPORT

A 57 year old white man came to me on April 4, 1939 complaining of stomach pain which had begun during the preceding fall. It was noted that this pain was more acute when his stomach was empty, and that eating gave relief from the pain. The taking of soda also gave relief. His sleep was frequently interrupted by epigastric pain which occurred irregularly between midnight and morning. There were no tarry stools. His only genitourinary complaint consisted of urgency and nocturia. He noted that the urinary stream was hard to start. He had lost about 10 pounds during the course of the present illness. His past history and habits gave no relevant facts. His father had died of paralysis, and his mother of "impaction of the bowels." Seven siblings were living and well. One brother had diabetes. One sister died of heart disease. One brother died of unknown cause, and one brother died of "creeping paralysis." The only positive physical findings were the presence of a bilateral pterygium, slight tenderness in the epigastric region, and a large prostate gland.

The story suggested peptic ulcer, but as the complaint appeared so late in life with absolutely no preceding stomach symptoms, it was realized that his symptoms might have been due to carcinoma of the stomach. He was referred to the hospital for roentgen-ray study. A roentgen-ray examination of the stomach made May 1 showed a large filling defect in the pre-pyloric region. In addition to this there was an oval shaped, translucent, movable mass in the stomach itself about two by three inches in diameter. A gastric analysis made at this time showed the gastric contents negative for occult blood. There were 31 degrees of free HCl, and 38 degrees total acidity. Twenty minutes after ingestion of a 7 per cent alcohol test meal, there were 76 degrees of free HCl and 80 degrees total acidity. Blood studies and urinalysis were completely normal.

From the above findings, a diagnosis of peptic ulcer was made. The movable, translucent mass in the stomach was considered to be a pedunculated epithelioma. An exploratory laparotomy was done on May 6, 1939. At operation, it was found that there was an ulcer on the greater curvature of the stomach about midway between the middle of the stomach and the pylorus. There was a large black hard foreign body found free in the lower end of the stomach. Operation consisted of removal of the foreign body with resection of the ulcer. The pathological report on the tissue removed was as follows: "This specimen shows a deep excavation with a rather sharp boundary. The floor of the ulcer consists of granulation tissue covered with a narrow zone of necrotic material, while deeper there is a considerable area of old scar tissue extending well into the muscle and at places extending to the epithelium. There is only a moderate amount of leukocytic infiltration in and beneath the ulcer and extending a short distance beneath the neighboring mucosa. There is no indication whatever of cancer. The brown mass accompanying the piece of stomach consists of necrotic material not identifiable."

From these findings the diagnosis was peptic ulcer probably due to phytobezoar. Inquiry after the operation revealed that the patient had eaten quite a large quantity of persimmons in the middle of an afternoon in the preceding fall just before the onset of the presenting symptoms. He had taken neither food nor water within several hours after the ingestion of the persimmons. The ulceration in his case evidently was due to the presence of the foreign body. Removal of the foreign body alone probably would have cured the ulcer, as that is the experience in most similar cases. However, he made an uneventful recovery, and has had no gastrointestinal complaints since operation.

CONCLUSIONS

1. Persimmon phytobezoars are formed in the stomach through the interaction of soluble shibuol and the gastric acids.
2. Such formations are aided by eating the whole persimmon, when the stomach is empty and no food or water is taken soon thereafter.
3. Phytobezoars may produce vague gastrointestinal symptoms and may cause ulceration of the gastric mucosa.
4. The diagnosis is made on the finding of a translucent mass in the stomach on roentgen-ray examination and upon the history of eating persimmons.
5. Treatment consists of surgical removal.
6. *Unpeeled persimmons should not be eaten when the stomach is empty.*

BIBLIOGRAPHY

1. IZUMI, ISIDA, and IWAMOTO: The mechanism of the formation of phytobezoars with special reference to persimmon ball, Jap. Jr. Med. Sci. Trans., 1933, ii, 21-35.

2. COPETTI, LUIGI: Two cases of phytobezoar, *Il Policlinico (Sez prat.)*, 1932, xxxix, 1005.
3. ALLEN, LEWIS G.: Phytobezoar: report of 3 cases, *Am. Jr. Roentgenol.*, 1938, xxxix, 67.
4. RUTLEDGE, C. P.: Phytobezoar of the stomach associated with gastric ulcer, *New Orleans Med. and Surg. Jr.*, 1937, xc, 35.
5. RODGERS, FLOYD D.: Phytobezoar of persimmon origin, *Radiology*, 1937, xxix, 494.
6. RAMSTAD, N. O.: Phytobezoar with gastric ulcer, *Journal-Lancet*, 1938, lviii, 505.
7. WYATT, WALTER S.: Phytobezoar, *Kentucky Med. Jr.*, 1932, xxx, 79.

ARTERIOLAR DISEASE OF THE HEART*

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ARTERIOLAR disease of the heart is relatively rare. In a large autopsy service it is occasionally found with the more severe grades of coronary arteriosclerosis. Plaut and Kramer¹ have reported a case of hyaline degeneration with extensive myomalacia and relatively intact coronary arteries. This report deals with a case of severe cardiac failure and complete heart block, with widespread medial hypertrophy of the arterioles of the heart, minimal changes of the larger coronary arteries, a diffuse thickening of the parietal endocardium, intact valves and microscopic necroses of the myocardial fibers.

CASE REPORT

The patient was a white man, 41 years old, of German descent, admitted to the City Hospital on July 9, 1935.

For 20 years he had suffered from cold hands, nose, ears and chin. Except for an attack of measles at the age of six, he had always been in good health. He was married and had one living child; his wife had had two miscarriages, both in the second month. In July 1922, he was examined for life insurance; no abnormalities were found; the pulse was 90, of good size, well sustained and regular. The blood pressure and urine were normal. In March 1923, a reëxamination was without significant findings. Venereal diseases were denied.

His present illness began in December 1933 with swelling of the feet, which would subside after short periods of rest in bed of two or three weeks. Weakness, dyspnea on the slightest exertion, and cough subsequently developed. He received treatment for cardiac dysfunction but the condition slowly progressed preventing him from carrying on his occupation of machinist. About January 20, 1935, the great toe of the left foot became swollen, red and tender. Soon the other four toes were affected and about a month later the great toe became ulcerated and discharged pus. On February 7, the great toe of the right foot became similarly involved and pain was constant. Two days later he was hospitalized.

Both feet were cold and cyanotic. All the toes of the left foot were gangrenous. Anterior tibial pulsation could not be felt. Both hands and the lower halves of the forearms were cold and cyanosed. The veins of the neck were dilated, and the pulsations, 110 per minute, were marked. The apex beat was visible and palpable in

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the fifth interspace 13.5 cm. to the left of the midline. The sounds were distant and of poor muscular quality and somewhat irregular. A loud blowing systolic murmur was heard over the apex and the base. The radial arteries felt thickened and sclerosed. The apical and radial pulses were equal in rate, 38 to 40 per minute. The blood pressure was, systolic 136, diastolic 98. The liver was palpable. The pupils were equal, regular, and reacted normally to light and in accommodation. The knee reflexes were normal. Fundus examination showed marked myopia; in the right eye patches of exudate, blurred disc margins and marked congestion were seen; in the left, the disc margins were raised, especially in the lower half, and a few patches of exudate were noted.

Roentgenography revealed an enlarged heart and pulmonary congestion. The blood Wassermann reaction was negative on two examinations. On admission, the non-protein nitrogen was 78 mg., and the uric acid 4.2 mg. per cent. In two weeks, the former had dropped to 36 mg. The urine was acid, its sp. gr. was 1.022; it contained 4 plus albumin, hyaline and finely granular casts, and red and white blood cells. The phenolphthalein excretion was 40 per cent in two hours. The Mosenthal test showed ability to concentrate to 1025.

On two occasions atropine was administered subcutaneously and he was observed over a six hour period. With a dose of 1/30 gr. the ventricular rate remained between 29 to 34, confirmed by electrocardiographic tracings. On the second occasion, one week later, the dose was increased to 1/15 gr. Within three hours he became delirious, the heart was unaffected, the rate remaining 31 to 35, and the respirations 26 to 30.

One week later 1 c.c. of 1-1000 adrenalin was given subcutaneously. Before administration the ventricular rate was 34, the blood pressure systolic 128 and diastolic 70. In fifteen minutes, the rate was 55, and the blood pressure 150/80. In five hours the rate fell to 34 and the blood pressure to 130/80.

He was discharged March 26, improved, with a diagnosis of obliterative endarteritis, heart block and chronic myocarditis.

On June 8 he returned to the hospital with the same complaints of cyanotic extremities and dyspnea on exertion. He remained for one month during which time his condition was not much changed. The heart findings were as before, the liver was palpable 8 cm. below the costal margin, the extremities were cyanotic, pulsation in the dorsalis pedis arteries was absent although there was no ankle edema. Both lungs had basal râles and there were signs of fluid in the right chest. Under digitalis he improved considerably. On discharge the liver was not palpable and he was free of dyspnea at rest.

On July 9 he was transferred to City Hospital where he remained until his death on October 5. The cervical venous pulsation was marked, with a ratio of three to one, the ventricular rate being 36. The pulses were full and the rate 36. The apex beat was in the sixth interspace, and the sounds were muffled. There was a distinct apical systolic and a questionable diastolic shock, but no thrills were felt. The blood pressure was 128 systolic and 64 diastolic. There was evident loss of weight, and the patient looked chronically ill. There was neither pain nor distress. The right pupil was irregular, and reacted normally to accommodation, sluggishly to light; the left was regular and reacted normally. An occasional moist râle was heard posteriorly at the right apex. The liver was palpable below the ensiform cartilage without pulsation or tenderness. There was no ascites. The extremities were slightly cyanosed. The Wassermann reaction was negative. The urea nitrogen measured 20 and 14 mg. per cent. The urine specific gravity was 1.024. It contained one plus albumin, a few waxy casts, and a very few white and red blood cells. The red blood cells numbered 5,400,000, and the white blood cells 9,500 with normal differential count. An electrocardiogram on July 10 showed complete heart block, an auricular rate of 90, and a ventricular rate of 34, QRS wide and notched, T_i inverted.

He remained in surprisingly good condition and was able to take a moderate amount of exercise without any undue symptoms. Fundal examination revealed opacities of both corneae, principally in the central and lower halves, obscuring the right fundus; the left disc was somewhat pale with choroidal changes due to myopia.

On September 23 the extremities were cyanosed, the blood pressure 144/90, and some moisture was present in the lung bases. An electrocardiogram (figure 1) showed complete auriculo-ventricular block; auricular rate of 108; ventricular rate

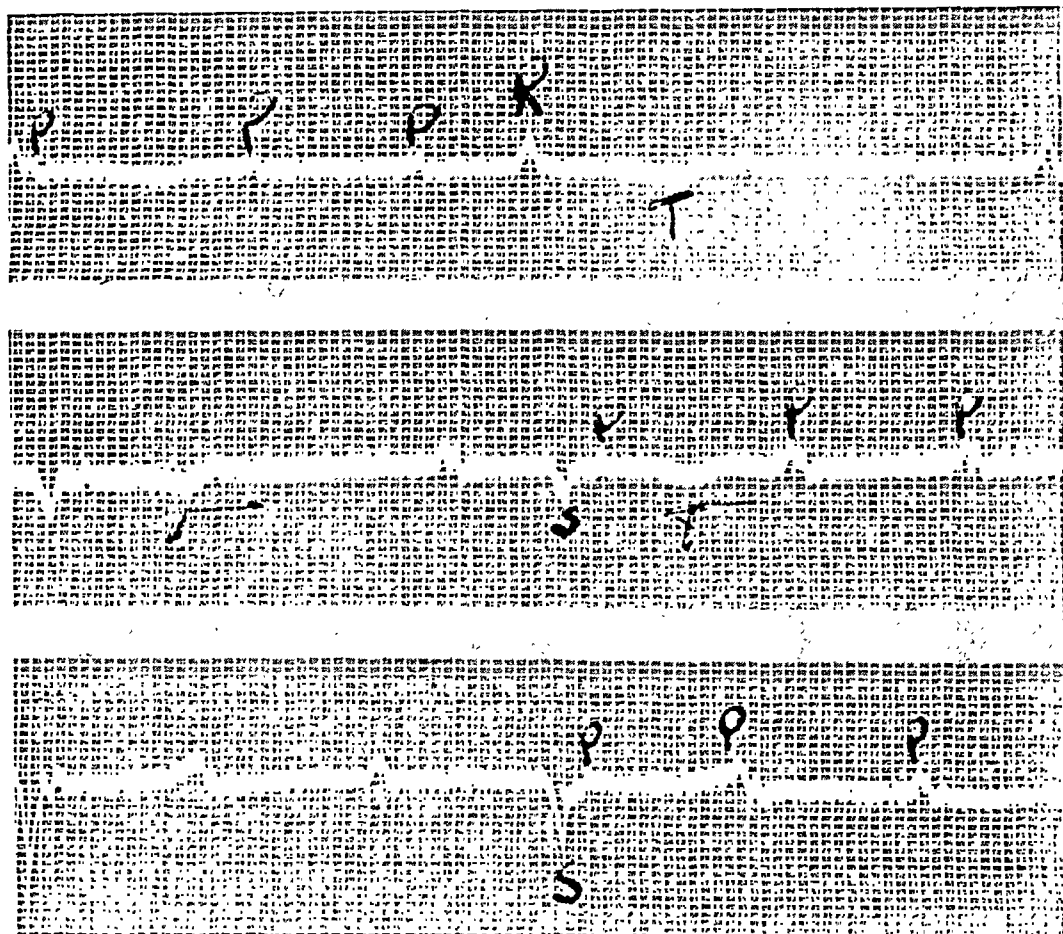


FIG. 1. Electrocardiogram taken September 23 showing complete heart block, intraventricular block and slight inversion of T_1 and T_2 .

of 36; the QRS wide, notched, slurred, 0.12 sec.; the S-T interval, 0.44 sec.; the T-waves low voltage; and slight inversion of T_1 and T_2 . Interpretation: complete heart block and intraventricular block.

He again improved but occasionally appeared mentally sluggish. On October 3, the right base was dull with diminished breath sounds and a few crackles. He was dyspneic, and the extremities were very cyanotic and cold. The pulse remained at 36. He was quite lethargic but clear periods were fairly common. On October 5, while talking, he became extremely cyanosed and died suddenly.

The temperature throughout remained between 97° and 99.6° F. and the pulse 32-40.

measured one cm. in thickness. The left auricle appeared normal. The left side of the interventricular wall showed an extensive diffuse white fibrosis of the endocardium extending from the base to the apex. The upper half measured 2 mm. in its thickest portion; in the lower half it was somewhat thinner and many abrupt thicker buttons were scattered over it. The process extended over the left ventricular endocardium but was more patchy in distribution and at the mitral sulcus, the involvement was minimal. Over the *columnae carnae* and papillary muscles the involvement was somewhat greater in degree. Small mural thrombi were present at the extreme apex.

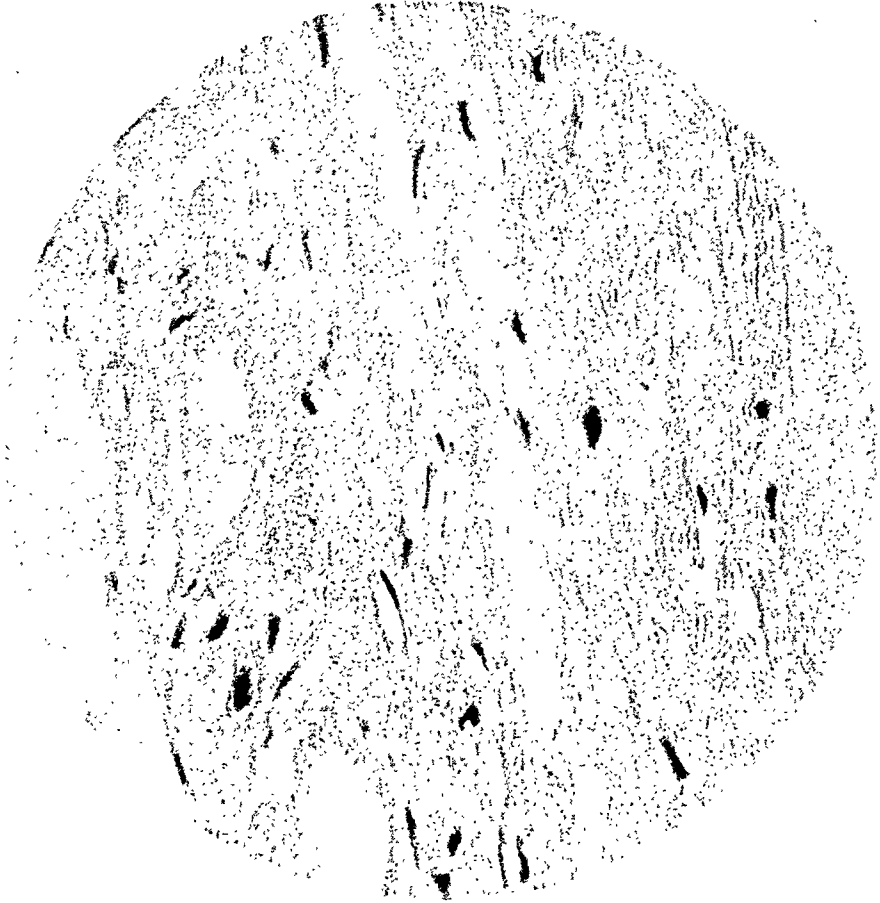


FIG. 3. Photomicrograph through the bifurcation of the bundle of His showing the marked fibrosis involving the branches with degeneration.

The myocardium showed a diffuse, fine, but rather inconspicuous fibrosis. The anterior descending coronary artery in its upper portion had one limited area of atheroma with narrowing of the lumen. The other arteries were remarkably free of change.

Microscopic examination: The endocardium was greatly thickened and fibrous, the fibrosis corresponding to the gross appearance, and involving the subendocardial areolar zone. In the thicker portions, elastic fibers were scanty or completely absent. In the regions of less marked involvement they were present in varying numbers and undergoing degenerative changes. Sometimes small inconspicuous foci of cellular reaction were seen in the deeper portions, usually in the regions of least involvement.

In the undefended space the endocardial fibrosis had involved the bifurcation of the bundle of His (figure 3) and the branches showed atrophy and degeneration. The main portion of the bundle was perfectly normal.

The hypertrophy of the myocardial fibers was much greater than the size or weight of the heart would indicate. It was generalized but more marked in the left ventricle and interventricular wall; in the right ventricle it was limited to the deep

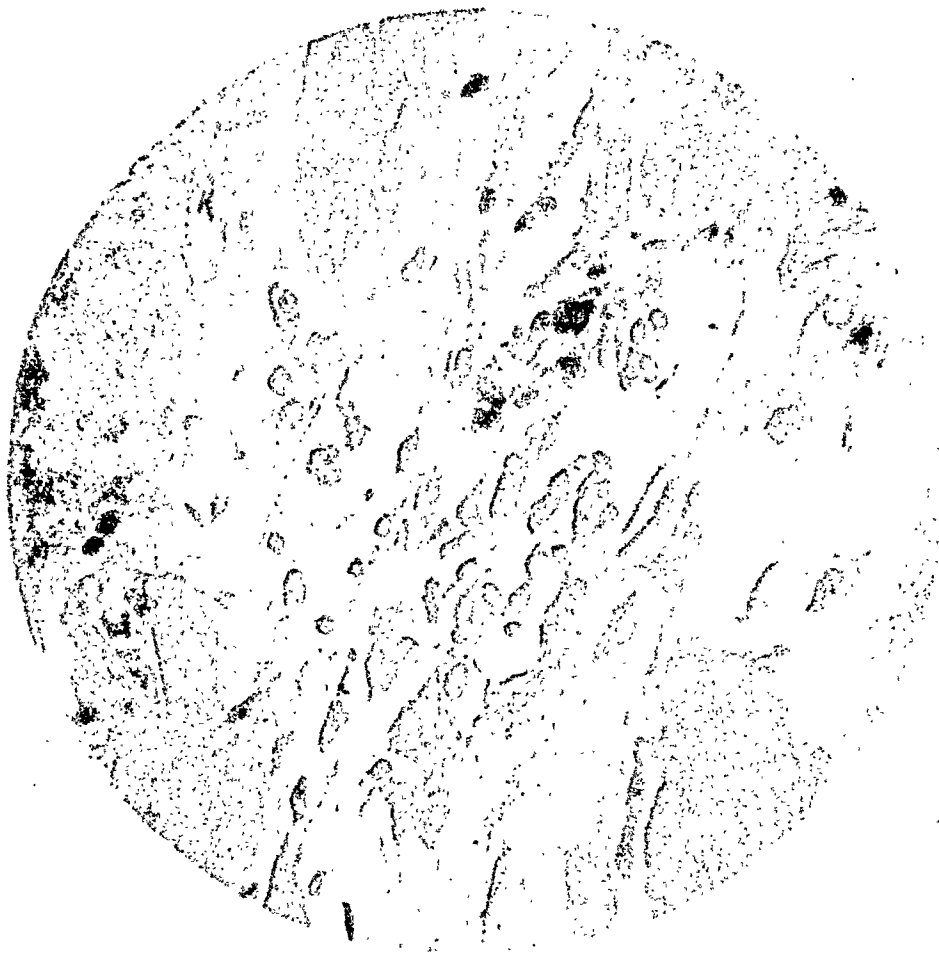


FIG. 4. Miliary necrosis of myocardial fiber with monocyctic and lymphoid infiltration and granular degeneration of the cytoplasm.

muscle layer. There was a fine diffuse scarring of all ages, cellular to hyaline. In the left side a few large scars were present. Focal necroses (figures 4 and 5) involving only portions of the myocardial fibers were extremely numerous. The cytoplasm was replaced by a granular mass infiltrated by polymorphonuclear leukocytes, monocytes, and lymphoid cells in varying proportion. Frequently individual foci had a pure cell infiltrate. Early fibrosis was present in some of the older lesions.

The larger coronary arteries showed very slight atheromatous changes. In a small portion of the left anterior descending artery was a large plaque. The arterioles (figure 6) exhibited an intense medial hypertrophy. Degenerative changes were

absent. The arteriolar change varied considerably in distribution. It was most marked in the left ventricle and interventricular wall corresponding closely to the diffuse scarring and acute myocardial necroses. Even in these walls, it varied considerably in different regions.

The valves were normal.

The other organs show nothing remarkable.

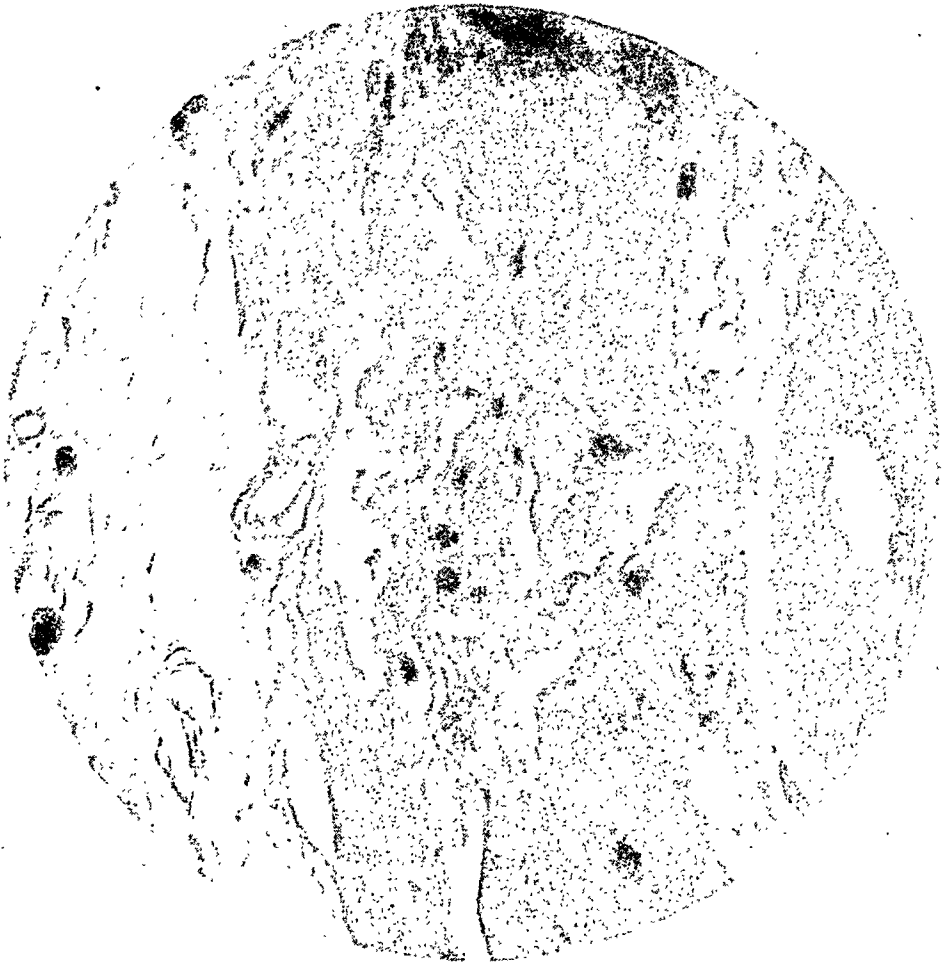


FIG. 5. Miliary necrosis of a myocardial fiber of slightly earlier phase.

Anatomical Diagnosis: Arteriolar disease of heart; acute multiple miliary necroses of myocardium; fibrosis of myocardium; chronic parietal endocardial fibrosis; heart block; general chronic passive congestion.

DISCUSSION

Many interesting clinical and pathological features distinguish this case. The course showed a relentless progress of cardiac dysfunction of rather short duration, less than one year, complete heart block, and peripheral cyanosis of the extremities presenting some evidence of periodicity. The more common

causes of heart block² are coronary arteriosclerosis, syphilis, rheumatic heart disease; the rarer are trauma, congenital heart disease, bacterial endocarditis, miliary tuberculosis and neoplasm. Syphilis, rheumatic heart disease, trauma, bacterial endocarditis and miliary tuberculosis could quite readily be eliminated on clinical grounds. Heart block in congenital cardiac disease is usually associated with a defect of the interventricular septum, no signs of which were ever

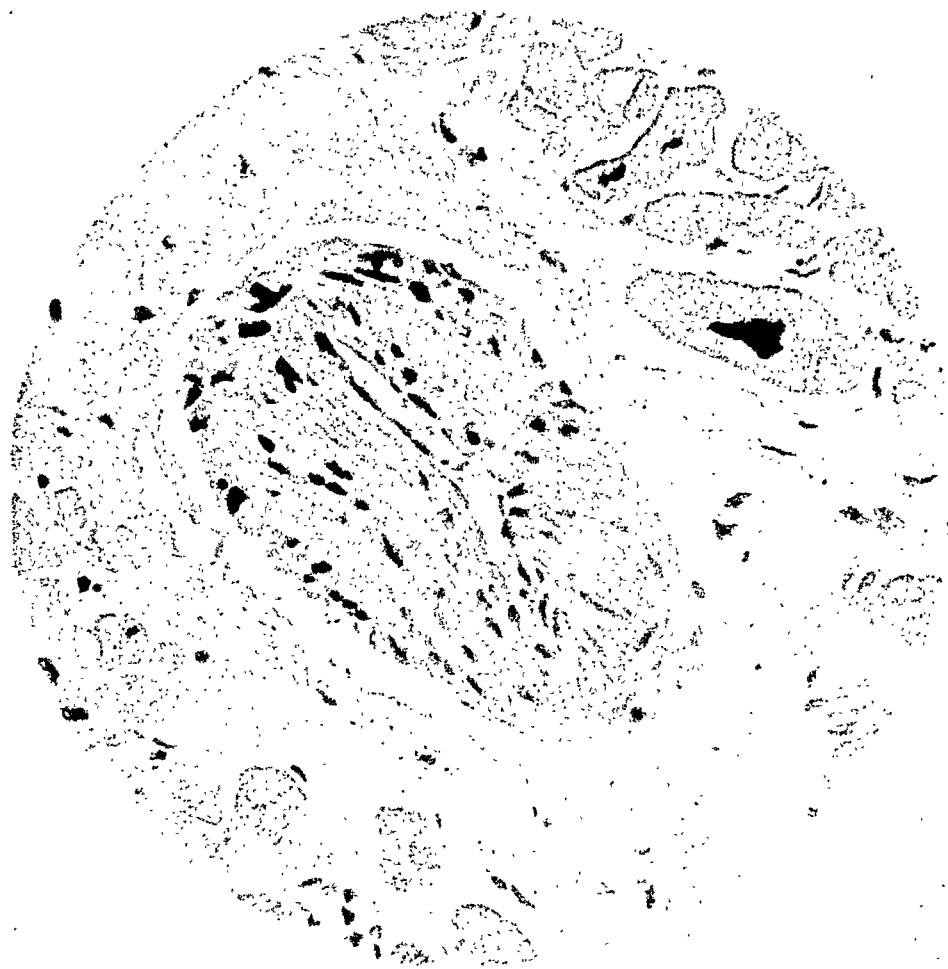


FIG. 6. Medial hypertrophy of arteriole of heart.

elicited in this case. Neoplasms occasionally cause it. They are most frequently metastatic and the original tumor has usually been productive of definite clinical symptoms while the cardiac signs are almost invariably terminal phenomena. Primary tumors of the heart causing block are much rarer; they usually are angiomas of the bundle and node and display clinically the Stokes-Adams syndrome. The peripheral symptoms displayed in the present case would also not be of help in an explanation of any of the usual causes of heart block. All these factors then could be eliminated as possible clinical diagnoses. Their elimination was confirmed by necropsy.

The most common cause of cardiac dysfunction is arteriosclerosis of the coronary arteries. At the age period of this patient, coronary arteriosclerosis is usually associated with a raised blood pressure due either to chronic glomerulonephritis or to essential hypertension. The absence of hypertension appeared to rule out both of these conditions. Arteriosclerosis of the coronary arteries on a non-hypertensive basis appeared remote. Such cases, as they come under our observation, are almost invariably in old individuals, the senile group, with marked evidence of the decrescent type of vascular disease. With any type of coronary arteriosclerosis, if peripheral lesions are present they seldom attack both arms and legs. On a clinical basis, therefore, although the diagnosis of coronary sclerosis could not be eliminated and seemed the most likely, it still left several questions unanswered. The necropsy demonstrated its absence.

Another diagnosis advanced was obliterative endarteritis. Pathologic data on the condition of the peripheral vessels are lacking so no definite opinion can be advanced. However, endarteritis usually attacks only the lower extremities. When it progresses to gangrene, such as was present early in this case, it seldom regresses to the degree found here. Nor is it commonly associated with cyanosis of the hands and forearms, a feature which was of some prominence. Its existence as an entity appears to rest on a somewhat insecure foundation.

There remains then another possibility to consider, that of Raynaud's disease. Here also the lack of pathologic data makes this only a tentative and not an absolute diagnosis. There are several points, however, which give this assumption some support. The patient, between the ages of 20 and 40, suffered from cold extremities. At the end of this period gangrene of the toes occurred and when he first came under hospital observation, coldness and cyanosis of both upper and lower extremities were striking. On each subsequent admission the same feature was present. Unfortunately the clinical examination of pulsation in the peripheral arteries was not noted between the periods of cyanosis, but from the available data the diagnosis of Raynaud's disease seems plausible.

Can Raynaud's disease be the factor underlying the unusual arteriolar disease of this heart? Hunt³ does not mention it as a possibility.

The hypothesis of Raynaud is that the vasomotor center is unduly irritable and that efferent impulses from the center lead to paroxysmal contraction of arterioles. As revealed by microscopy, the arterioles presented a marked medial hypertrophy suggestive of some overactivity of the muscular wall. Peripheral vascular changes only have been described in Raynaud's disease, none of the cardiac arterioles. In essential hypertension, however, changes in the smaller arteries of the body of a somewhat similar character are found, viz. reduplication of the internal elastic lamella. Although medial hypertrophy of the coronary arterioles is unusual in essential hypertension, it has been observed in some instances in material at the laboratory of the City Hospital. It probably represents work hypertrophy. The paroxysmal contraction in Raynaud's disease could also result in medial hypertrophy, similarly a work hypertrophy from another cause. On this basis therefore it seems not unreasonable to look upon the cardiac vascular changes as having some relationship to Raynaud's disease.

There remains then the explanation of the myocardial and endocardial changes. If the case is one of vasoconstriction with an attendant hypertrophy affecting the cardiac arterioles, spasm leading to anoxemia could result in myocardial necrosis followed by cellular reaction and fibrosis producing the his-

tological changes encountered. Involvement of the subendocardial zone of muscle, a condition also found in this heart, could likewise result in the parietal endocarditis. Endocardial fibrosis over an old infarct, which is simply necrosis on a massive scale, is a commonly recognized sequel. The cause of the heart block is evident, involvement of both branches at the bifurcation by scar.

There is still one other feature to be considered, the terminal episode of sudden death. The death appears certainly to have been cardiac and quite probably due to ventricular fibrillation. In a previous communication⁴ it has been suggested by one of us (J. R. L.) that the summation of ectopic beats from multiple foci of hyperirritability due to recent myocardial damage may result in ventricular fibrillation. The conditions present in this case appear to fit this theory.

SUMMARY AND CONCLUSIONS

A case of arteriolar disease of the heart of unusual character is reported. The course was that of relentless progress of cardiac dysfunction, complete heart block and signs suggestive of Raynaud's disease. The necropsy showed medial hypertrophy of the arterioles of the heart, minimal changes of the larger coronary arteries, diffuse fibrosis of the parietal endocardium, intact valves and microscopic necroses of the myocardial fibers. The hypothesis is advanced that the arteriolar changes of the heart are directly related to Raynaud's disease and that these changes are causative factors in the myocardial degeneration and endocardial fibrosis. The heart block appears to have been due to involvement of the branches at the bifurcation of the bundle of His by the endocardial scarring.

REFERENCES

1. PLAUT, A., and KRAMER, M. L.: Arteriolar disease of the heart, *Arch. Path.*, 1936, xxiii, 393.
2. WHITE, P. D.: *Heart disease*, 1935, Macmillan Co., New York, p. 673.
3. HUNT, J. H.: The Raynaud phenomena: a critical review, *Quart. Jr. Med.*, 1936, xxix, 399.
4. LISA, J. R.: Pathological changes in the heart in sudden cardiac death, *ANN. INT. MED.*, 1938-39, xii, 1968.

EDITORIAL

"HYPERINSULINISM" AND "SPONTANEOUS HYPOGLYCEMIA"

DURING recent years there have been two advances in our knowledge of hyperinsulinism. The first is the report of additional proved cases of this interesting condition; the second is the increasing insistence that the term hyperinsulinism be reserved for those cases in which there is proof that the symptoms are caused by the excessive production of endogenous insulin. In all other cases in which hypoglycemia is a finding the condition should be diagnosed as "spontaneous hypoglycemia."

True hyperinsulinism is a rare disease. Frantz,¹ who recently reviewed the world literature, found only 96 cases in which the diagnosis had been proved at operation or necropsy.

Hypoglycemia, on the other hand, is much more common and may be present either "physiologically" or owing to any one of many disturbances in carbohydrate metabolism. It may be related to a disorder in absorption or utilization of food as in certain diseases of the liver or due to a disturbance in those glands concerned directly or indirectly with carbohydrate metabolism. Hypoglycemia has been reported in connection with disturbances in the nervous system or the thyroid, adrenal, pituitary and sex glands. Not always, however, is the degree of hypoglycemia sufficiently severe to produce significant symptoms. Meakins² reported three cases of postencephalitic Parkinson's disease in which attacks of convulsions were associated with low concentrations of sugar in the blood. He urged further search for other cases in which a connection between a hypothalamic lesion and hypoglycemia was suggested. Adlersberg and Friedman,³ who reported on disturbances of carbohydrate metabolism in 21 cases of postencephalitic Parkinson's disease, observed pathologically low levels of sugar in the blood in only three cases and these levels were observed after administration of 50 gm. of glucose. Hypoglycemia was reported by Rathery, Dérot and Sterne⁴ in two cases of subdural hemorrhage and by Birnbaum and Wood⁵ in cases of general paralysis.

Hypoglycemia may be present in many cases without organic disease. Matthews⁶ determined the postabsorptive concentration of sugar in the blood of 117 normal persons and found that it ranged from 0.06 to 0.11 gm. per 100 c.c.; in 70 per cent the values fell between 0.07 and 0.08 gm. Hart

¹ FRANTZ, V. K.: Tumors of islet cells with hyperinsulinism; benign, malignant and questionable, *Ann. Surg.*, 1940, cxii, 161.

² MEAKINS, J. C.: Hypoglycemia following encephalitis, *Ann. Int. Med.*, 1940, cxiii, 1830.

³ ADLERSBERG, D., and FRIEDMAN, R.: Quoted by Meakins, J. C.

⁴ RATHERY, F., DÉROT, M., and STERNE, J.: Hypoglycémie dans deux cas d'hémorragie méningée sous-arachnoidienne, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1931, xlvii, 1578.

⁵ BIRNBAUM, LEO, and WOOD, J. A.: Hypoglycemia as a cause of seizures in general paralysis, *Med. Bull. Vet. Admin.*, 1938, xiv, 236.

⁶ MATTHEWS, M. W.: A study of the one dose three hour (standard) and the two dose one hour (Exton-Rose) glucose tolerance tests, Thesis, University of Minnesota, 1939.

and Lisa⁷ analyzed all determinations of blood sugar made over a six year period at City Hospital, New York City. The data included routine determinations in 21,000 cases. In about 11 per cent the concentration of blood sugar was less than 0.08 gm. per 100 c.c.; in 7 per cent, between 0.070 and 0.079 gm.; in 2.3 per cent, between 0.060 and 0.069 gm.; in 0.8 per cent between 0.050 and 0.059 gm. and in 0.4 per cent less than 0.050 gm. Symptoms were absent in the entire group with the exception of one case in which the level of blood sugar was 0.030 gm.

Sufficiently strenuous exercise may produce severe hypoglycemia even among trained and healthy athletes.^{8, 9} Patients who are nervous or high-strung seem less able than others to withstand effectively the strain placed on the homeostasis of the blood sugar by exercise. Michael performed several determinations of the concentration of sugar in the blood of each of 30 golfers in the course of 18 holes of golf after they had eaten their usual luncheon.¹⁰ The values dropped to hypoglycemic levels (the average value was 0.054 gm. per 100 c.c.) between the ninth and fifteenth holes, or about two hours after the meal. The hypoglycemic period corresponded to a period of fatigue, mild symptoms of hypoglycemia and lessened efficiency, as reflected by poorer scores. Both the hypoglycemia and severity of symptoms were exaggerated among the poorer golfers, apparently because of tension, anxiety and greater output of energy, and were far less marked than average among the expert golfers, who were usually well poised and relaxed. A second observation was made on the same group after they had eaten food which contained more fat and less carbohydrate; consumption of sugar or candy at the seventh and eighth holes resulted in elimination of both hypoglycemia and its symptoms, and produced much better scores.

The term hyperinsulinism, then, should be reserved for those rare patients suffering from a serious disease, the result of the excessive secretion of insulin from a tumor of the islands of Langerhans; such patients should be subjected to surgical exploration. Thousands of other persons have varying degrees of hypoglycemia, with varying and usually vague complaints, caused by any one of many conditions. Hypoglycemia is not, in itself, a serious problem; such patients require, at most, more frequent feedings.

E. H. RYNEARSON

⁷ HART, J. F., and LISA, J. R.: The rate of occurrence of hypoglycemia; a study of 21,000 routine fasting blood sugars, *Endocrinology*, 1940, xxvii, 19.

⁸ LEVINE, S. A., GORDON, BURGESS and DERICK, C. L.: Some changes in the chemical constituents of the blood following a marathon race, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 1778.

⁹ JOKL, ERNST: *Sportärztliche Kasuistik*, *Klin. Wchnschr.*, 1933, xxii, 912.

¹⁰ MICHAEL, PAUL: Blood sugar studies on golfers, *Jr. Am. Med. Assoc.*, 1940, cxv, 286.

REVIEWS

The Heart in Pregnancy and the Childbearing Age. By BURTON E. HAMILTON, M.D., K. JEFFERSON THOMSON, M.D., and FREDERICK C. IRVING, M.D., F.A.C.S. 402 pages; 24 × 16 cm. Little, Brown and Co., Boston. 1941. Price, \$5.00.

Many consulting internists have had the uneasy sensation that their knowledge concerning the behavior of the damaged heart in pregnancy was inadequate because of lack of sufficient experience with such cases during late pregnancy, labor and the puerperium. The problem of predetermining the risks of pregnancy to the cardiac is not one which should be assumed lightly. Even more difficult without specialized experience is the determination during pregnancy of the significance in the cardiac of certain changes in signs and symptoms. The decision as to the continuation of pregnancy and as to the relative risks of interrupting pregnancy and of carrying patients to term is a vital one.

The authors present the carefully studied experience of the Heart Clinic associated with the Boston Lying-In Hospital. It is the reviewer's belief that no more valuable addition to the working library of the practitioner, internist, cardiologist, or obstetrician has been made in recent years. The volume is divided into three books. Book I deals first with factual data as to incidence of cardiac disease among pregnant women, the classification of such cardiac cases, prognosis, etc. In Chapter 2 the causes of cardiac failure in pregnancy, the signs of failure, and the treatment of the cardiac are detailed. The methods of delivery (Dr. F. C. Irving) are discussed in the third chapter, and postpartum complications and after care are included in the fourth chapter.

Book II gives an extremely interesting account of what is known concerning the physiology of the circulation in normal pregnancy and in pregnant women with heart disease.

Book III takes up in eight chapters specific data concerning special types of heart disease in relation to the strain of pregnancy. The experiences of the authors and the literature of the subject are surveyed to round out the figures necessary for a statistical approach to the risks involved. Often available data are still insufficient. The chapter on congenital heart lesions includes data from the series of Dr. Maude Abbott.

The authors have made a contribution which will directly assist all physicians who have to deal with the pregnant cardiac. Moreover, it will stimulate others to consider more carefully the still unsolved problems in this field.

M. C. P.

Diseases of the Gallbladder and Bile Ducts. By WALTMAN WALTERS, B.S., M.D., M.S. in Surgery, Sc.D., F.A.C.S., and ALBERT M. SNELL, B.S., M.D., M.S. in Medicine, F.A.C.P. 645 pages; 24.5 × 16 cm. W. B. Saunders Co., Philadelphia. 1940. Price, \$10.00.

The diseases of the gall-bladder and of the biliary tract are of particular interest to the internist. His experience with these conditions is large, and very frequently the results obtained are unsatisfactory. This volume presents the studies, the clinical methods and the results obtained in a Clinic which for half a century has had an exceptional group of physiologists, internists and surgeons who have devoted much time to the investigation and care of an extraordinarily large series of patients with biliary disease. The internist will profit by reading such a monograph and will find it useful for consultation on special topics. It is not an exhaustive treatise but it covers all important points adequately, and the references to the literature are sufficiently abundant for any necessary supplementary reading. It has the invaluable quality of

presenting problems from a practical working point of view which gives the reader some of the perspective of the authors as to the relative importance of certain facts and theories in this often confused field.

Part I is a relatively brief and very interesting review of the medical history and of the anatomy, physiology, pathogenesis and pathology of diseases of the gall-bladder and bile ducts. Part II is devoted to diseases of the gall-bladder; Part III to diseases of the bile ducts; Part IV to medical and surgical treatment; and Part V to pre-operative and postoperative care. There is an appendix on technic. In addition to the chief authors who represent the surgical and medical interests in this field there are contributing authors who present special aspects.

The quality of the book is such that it should be in every hospital library. House officers and staff alike will find it valuable for consultation in relation to their daily problems in the diagnosis and treatment of diseases of the biliary tract.

M. C. P.

Diagnosis and Treatment of Menstrual Disorders and Sterility. By CHARLES MAZER, M.D., F.A.C.S., and S. LEON ISRAEL, M.D., F.A.C.S. 485 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. 1941. Price, \$6.50.

The authors have furnished in this volume a very compact and complete discussion of their subject. This book should be invaluable to the general practitioner, specialist, and to one who wants a quick but accurate reference. The medical student should use this book only for reference as the scope is too wide for his limited knowledge.

The general disorders are discussed in a systematic manner, each in a separate unit which includes etiology, signs, symptoms and treatments. The treatments are discussed in detail, giving illustrations, case histories, technic and the exact doses of medication. The illustrations are very accurate and informative. A very important addition are the chapters on male sterility which are rather lengthy and well organized. This phase of the problem is often overlooked by many authors in discussing this subject, or they pass over it lightly.

The main difficulty with this discussion, as in many others of the day, is that so much of the treatment deals with endocrines which at the present time are in a constant state of flux. On the whole, the authors have covered the field thoroughly and have put into one volume the accepted and important knowledge of the subject.

The bibliography is excellent, and the appendix, containing dosages and potency of the various endocrine preparations, is a valuable adjunct.

E. I. C., JR.

Chemotherapy and Serum Therapy of Pneumonia. By FREDERICK T. LORD, M.D., ELLIOTT S. ROBINSON, M.D., and RODERICK HEFFRON, M.D. 174 pages; 21.5 × 14 cm. The Commonwealth Fund, New York. 1940. Price, \$1.00.

This is the third in a series of handbooks on pneumonia therapy published by this Fund. The present edition includes chemotherapy as well as additional data on the use of horse and rabbit antiserum.

Diagnosis, typing and immunity factors are discussed somewhat briefly but in a quite adequate manner. The treatment with serum and chemotherapy is presented exceptionally well; exact methods of administration, precautions and dangers are clearly brought out.

The arrangement of the book is somewhat different from usual, inasmuch as the important headings are set forth in bold type in the margin of the page.

This book is highly recommended, and anyone treating pneumonia will find it an asset to his library.

W. K. W.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

- Lt. Col. Daniel B. Faust, F.A.C.P., (MC), U. S. Army—"Diet Manual, Fitzsimons General Hospital";
Dr. David Warren Kramer, F.A.C.P., Philadelphia, Pa.—"Manual of Peripheral Vascular Disorders."

Reprints

- Dr. Robert S. Berghoff, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Darrell C. Crain, Jr. (Associate), Washington, D. C.—1 reprint;
Dr. Norbert Enzer, F.A.C.P., Milwaukee, Wis.—3 reprints;
Dr. Irvin R. Fox (Associate), Eugene, Ore.—1 reprint;
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—1 reprint;
Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—1 reprint;
Dr. Saul Jarcho (Associate), New York, N. Y.—5 reprints;
Dr. Edward S. King, F.A.C.P., Wake Forest, N. C.—2 reprints;
Dr. Edward Kupka, F.A.C.P., Olive View, Calif.—2 reprints;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—2 reprints;
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—5 reprints;
Dr. J. Arthur Myers, F.A.C.P., Minneapolis, Minn.—15 reprints;
Dr. Louis B. Owens (Associate), Cincinnati, Ohio—1 reprint;
Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Lt. Col. James S. Simmons, F.A.C.P., (MC), U. S. Army—1 reprint;
Dr. Hugh Stalker, F.A.C.P., Detroit, Mich.—1 reprint;
Dr. Frederick Tice, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—1 reprint;
Dr. Oscar T. Wood, Jr. (Associate), Bywood, Pa.—2 reprints.

REGIONAL MEETING OF FLORIDA MEMBERS OF THE COLLEGE

On April 28 the Florida members of the American College of Physicians held their annual meeting in Jacksonville, Fla. The following program was presented:

Dr. James L. Borland, F.A.C.P., and Dr. Lucien Y. Dyrenforth, F.A.C.P., Jacksonville—"Erythrocyte Sedimentation Rate: A Comparative Analysis Based Upon Routine Clinical Data";

Dr. Karl B. Hanson (Associate), Jacksonville—"The Use of Cobra Venom and of Oxygen in the Control of Cardiac Pain";

Dr. J. Webster Merritt, F.A.C.P., Jacksonville—"Electrocardiographic T Wave Changes in Nonorganic Heart Disease."

Dr. Turner Z. Cason, F.A.C.P., Jacksonville, is the College Governor for Florida; Dr. Louie Limbaugh, F.A.C.P., Jacksonville, is President and Dr. Kenneth Phillips, F.A.C.P., Miami, is Secretary of the Florida Chapter.

The 13th Annual Spring Clinical Conference of the Dallas Southern Clinical Society was held at Dallas, March 17-20, under the presidency of Dr. Everett C. Fox, F.A.C.P., Dallas, Tex. Among the especially invited guests were the following:

Dr. Soma Weiss, F.A.C.P., Boston, Mass., four addresses—"Physiology and Interpretation of Common Symptoms in the Practice of Medicine," "New Drugs and New Uses of Old Drugs," "Etiology of Essential Hypertension," and "Pharmacologic Action and Clinical Use of Drugs Acting on the Autonomic Nervous System";

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Pa., three addresses—"Pitfalls in X-Ray Diagnosis," "Hodgkin's Disease," and "Roentgen Analysis of Fractures";

Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill., three addresses—"Sub-clinical States of Deficiency Diseases," "Diet in Medical Practice," and "Management of Obesity."

Dr. Nathan B. Van Etten, F.A.C.P., New York, N. Y., President of the American Medical Association, spoke on "American Health and National Defense" at a recent meeting of the Medical Society of the County of Kings and Academy of Medicine of Brooklyn.

The Board of Corporators of the Woman's Medical College of Pennsylvania recently appointed Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J., Acting President of the College, following the resignation of Dr. Chevalier Jackson.

Dr. Archibald A. Barron, F.A.C.P., Charlotte, was elected President, and Dr. Fonso Butler Watkins, F.A.C.P., Morganton, Vice-President of the North Carolina Neuropsychiatric Association at its recent meeting at Durham, N. C. Dr. Barron succeeds Dr. Mark A. Griffin, F.A.C.P., Asheville. Dr. Walter Freeman, F.A.C.P., Washington, D. C., gave the principal address at this meeting. He spoke on prefrontal lobotomies, a surgical operation on the brain which has produced beneficial results in certain cases of depression.

Dr. James L. McCartney, F.A.C.P., Philadelphia, Pa., Associate Director of the Medical Division of Sharp & Dohme, Inc., and Editor of the "Sharp & Dohme Seminar," has been appointed Medical Director of William R. Warner & Co., Inc., New York, N. Y., and affiliate organizations, effective April 1, 1941. Dr. McCartney graduated from Rush Medical College, University of Chicago, and has been associated with Sharp & Dohme since 1938. In his new position, Dr. McCartney will be chief medical advisor to William R. Warner & Co., Inc., and in charge of clinical research, in coöperation with the Warner Institute for Therapeutic Research, which is under the direction of Dr. M. R. Thompson.

Recently the British Medical Association gave a private luncheon in honor of Dr. Thomas Parran, F.A.C.P., Surgeon General, U. S. Public Health Service, Dr. John E. Gordon, F.A.C.P., Boston, Mass., who is acting as U. S. Liaison Officer with the Ministry of Health, and Dr. John R. Mote, who is now acting as Medical Advisor to the American Red Cross Committee in London. Sir Wilson Jameson, Chief Medical Officer to the Ministry of Health, was the other guest, and among those present were the principal officers and officials of the Association.

On March 17 Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, Pa., spoke on "The Reticulo-Endothelial System in Clinical Medicine" at a meeting of the Medical Officers of the War Department of the U. S. Army, Washington, D. C.

Dr. John M. Dyson, F.A.C.P., Hazleton, Pa., addressed a recent meeting of the Columbia County Medical Society at Berwick, Pa., on "Modern Treatment of Pneumonia."

Dr. Arthur J. Logie, F.A.C.P., Jacksonville, Fla., was the guest speaker at a meeting of the Leon County Medical Society at Tallahassee, Fla., on March 18, 1941. Dr. Logie spoke on "More Recent Advances in the Diagnosis of Tuberculosis."

Dr. Thomas J. Longo, F.A.C.P., Brooklyn, N. Y., has been elected Director of Medicine at the Coney Island Hospital, Brooklyn.

Dr. Albert E. Russell, F.A.C.P., New York, N. Y., has been promoted to the grade of Senior Surgeon in the U. S. Public Health Service. Dr. Russell has recently been assigned to the Army Second Corps Area at Governors Island, N. Y.

Among the speakers at the 31st meeting of the Brooklyn Society of Internal Medicine, held at the Methodist Hospital, Brooklyn, N. Y., were:

Dr. Henry D. Fearon, F.A.C.P., Brooklyn, N. Y.—"Remarks on Sulfathiazole";

Dr. Harold R. Merwarth, F.A.C.P., Brooklyn, N. Y.—"The Occurrence of Peripheral Facial Paralysis in Hypertensive Vascular Disease."

On April 16, 1941, Dr. Ralph Pemberton, F.A.C.P., Paoli, Pa., addressed the Medical Society of the District of Columbia, Washington. On April 30, 1941, Dr. Pemberton addressed the Long Island College Hospital Staff, Brooklyn, N. Y.

The American Academy of Physical Medicine held its 19th annual meeting and scientific session in New York, N. Y., April 28-30, 1941. Among the speakers at this meeting were:

Dr. Walter M. Solomon (Associate), Cleveland, Ohio—"Treatment of Epidermophytosis by Iontophoresis";

Dr. Irving Sherwood Wright, F.A.C.P., New York, N. Y.—"Physical Measures in Peripheral Vascular Disease";

Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—"Disabilities Encountered Among Veterans";

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn.—"Methods of Applying Heat Locally in General Practice."

Dr. Anthony C. Cipollaro, F.A.C.P., New York, N. Y., conducted a panel discussion on "Physical Medicine in Dermatology."

Among those who participated in a series of Friday afternoon lectures of the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn were:

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y.—"The Treatment of Infectious Arthritis," March 14, 1941;

Dr. Priscilla White, F.A.C.P., Boston, Mass.—"The Diabetic Child," March 28, 1941;

Dr. Frank Bethel Cross, F.A.C.P., Brooklyn, N. Y.—"Hypertension: Its Renal and Psychogenic Aspects," April 4, 1941.

The following members of the College presided at the round-table therapeutic reviews of this society:

Dr. Edwin P. Maynard, Jr., F.A.C.P., Brooklyn, N. Y.—“Treatment of Angina Pectoris and Coronary Thrombosis”;

Dr. John H. Crawford, F.A.C.P., Brooklyn, N. Y.—“Treatment of Congestive Heart Failure”;

Dr. Charles Solomon, F.A.C.P., Brooklyn, N. Y.—“The Use and Abuse of Hypnotics and Sedatives.”

Dr. Maurice J. Dattelbaum, F.A.C.P., is President; Dr. Benjamin M. Bernstein (Associate), Associate Secretary; Dr. Abraham Klein, F.A.C.P., Associate Treasurer; and Dr. Edwin P. Maynard, Jr., F.A.C.P., Associate Directing Librarian and Curator of this society.

The following members of the College addressed recent meetings of the Medical Society of the District of Columbia, Washington:

Dr. E. Gurney Clark (Associate), Baltimore, Md.—“Clinical Epidemiology in the Management of Syphilis,” April 2, 1941;

Dr. Charles R. L. Halley (Associate), Washington, D. C.—“The Clinical Diagnosis of Syphilis,” April 2, 1941;

Dr. Worth B. Daniels (Associate), Washington, D. C.—“An Outbreak of Bronchopneumonia in a Girls' School,” April 16, 1941;

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn.—“Differential Diagnosis of Psychoneuroses,” April 21, 1941.

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., who has been Acting Dean of Yale University School of Medicine since the retirement of Dr. Stanhope Bayne-Jones in 1940, was appointed Dean, effective July 1, 1941. Dr. Blake joined the medical faculty of Yale as John Slade Ely Professor of Medicine in 1921 and served with that title until 1927, when he became Sterling Professor of Medicine.

Dr. George R. Minot, F.A.C.P., Boston, Mass., recently addressed the Essex County Medical Society at Newark, N. J., on “Etiology, Diagnosis and Treatment of the Anemias.”

The annual Alumni Postgraduate Session and the Ernst A. Sommer Memorial Lectures of the University of Oregon Medical School, Portland, Ore., were given March 17–21, 1941. Dr. William S. Middleton, F.A.C.P., Madison, Wis., lectured on “Further Rationalized Therapeutic Experiences” and “Infectious Arteritis.” During this Session Dr. Middleton led a luncheon round-table discussion on “Cardiac Emergencies.”

Among the speakers at a recent meeting of the New York and Philadelphia Chapters of the National Gastroenterological Association, held in Philadelphia, Pa., were:

Dr. Anthony Bassler, F.A.C.P., New York, N. Y.—“Recent Advances in Gastroenterology”;

Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—“Recent Advances of Hepatic Function Tests”;

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Pa.—“Therapeutic Use of Cholesterol Ester Sol in Infectious and Toxemic Diseases.”

The 9th annual Postgraduate Clinic of the George Washington University School of Medicine was held recently in Washington, D. C. Dr. Tom D. Spies, F.A.C.P.,

Cincinnati, Ohio, spoke on "Clinical Aspects of Nutritional Diseases," and Dr. Paul D. White, F.A.C.P., Boston, Mass., conducted a clinic on heart diseases at this meeting.

The 26th annual meeting of the Iowa Tuberculosis Association was held in Des Moines, Iowa, March 27-28. Among the speakers at this meeting were:

Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill.—"Trends During the Past Decade in the Management of Tuberculosis";

Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—"A Challenge to Iowa Colleges."

The annual Russell D. Carman Lecture was presented under the auspices of the St. Louis (Mo.) Medical Society on March 25, 1941. Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., gave the Lecture. His subject was "Cancer of the Gastrointestinal Tract: Its Early Manifestations."

Dr. Howard F. Root, F.A.C.P., Brookline, Mass., was one of the guest speakers at a meeting of the Philadelphia County Medical Society on March 12, 1941. Dr. Root spoke on "The Possibilities of Cure of Diabetes."

The National Tuberculosis Association, 1790 Broadway, New York, N. Y., will furnish, free to physicians, a copy of "Chest X-Ray Interpretation," by Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., upon request. This publication is made available in connection with the National Tuberculosis Association's 1941 campaign.

OBITUARIES

DR. HARRY BEECHER McCORKLE

On December 25, 1940, Dr. Harry Beecher McCorkle died in California of bronchopneumonia following influenza.

Dr. McCorkle was born in Coffeyville, Kansas, August 1, 1870. He attended the State University at Lawrence, Kansas, and was graduated in 1898 in Medicine from the St. Louis University School of Medicine then known as Marion-Sims College of Medicine.

He had a large practice in Colorado Springs for over 30 years. He had been a member of the general staff of the Glockner Hospital, Beth-El Hospital and Beth-El Sanatorium for many years. He was medical director of the National Methodist-Episcopal Sanatorium for Tuberculosis and specialist on tuberculosis for the Missouri-Pacific Hospital Association and Brotherhood of Railway Trainmen. He was a member of the El Paso County Medical Society, the Colorado State Medical Society, the American Medical Association, and the American College of Physicians. He was a member of the Masonic Lodge and the Knights of Pythias.

During his early life, he met and knew many of the interesting personalities famous in the early history of the Southwest. It is stated that he was in Coffeyville, Kansas, on the day the Dalton boys held up the town.

After receiving his medical degree, he returned to Oklahoma and prac-

ticed medicine at Billings for about ten years, during most of which time he was mayor of that city.

About the year 1910 he developed pulmonary tuberculosis and came to Colorado Springs where he was a patient in the Modern Woodmen Sanatorium for many months. After recovery he started practice in Colorado Springs and was very active in his profession until December, 1939, when he was forced to retire because of poor health.

Soon after his graduation from medical college, he married Miss Edna V. Becker. Mrs. McCorkle and three children survive; the children are Mrs. Cora McCluskey of Santa Rosa, California; Mrs. Helen Warner, Wickenburg, Arizona, and Jack McCorkle of Los Angeles, California. He is also survived by one brother and one sister who live in Oregon and Kansas, respectively.

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado

DR. DANIEL E. S. COLEMAN

Dr. Daniel E. S. Coleman, F. A. C. P., New York City, died February 27, 1941, at the age of sixty-eight.

Dr. Coleman was born in New York City, July 20, 1872, attended the University Grammar School, St. Louis College, and De La Salle Institute. He received the degree of Ph.B. from St. Francis Xavier College in 1894, and his M.D. degree from the New York Homeopathic Medical College and Flower Hospital in 1901. After an internship at the Metropolitan Hospital, he held the following appointments: Anesthetist, 1903-04, Ophthalmic Hospital; Visiting Physician, 1904-09, St. Gregory Hospital; Consulting Physician, 1909-13, same; Assistant Visiting Physician, 1906-15, Metropolitan Hospital; Visiting Physician, 1915-28, same; Assistant Visiting Physician, 1904-13, Flower Hospital; Visiting Physician 1913-19, same; Instructor, Lecturer and Professor of Materia Medica, 1904-19, New York Homeopathic Medical College. In more recent years he was Senior Attending Physician and Secretary of the Board of Directors of the Community Hospital (Welfare Island).

For many years Dr. Coleman was a commissioned Major in the Medical Corps of the National Guard. He made many contributions to medical literature, some of them appearing as late as 1939. He was a former President of the American Association of Clinical Research, twice President of the Alumni Association of New York Homeopathic Medical College and Flower Hospital, a former President of the International Hahnemannian Society; member, Association of Military Surgeons of the U. S. A., American Institute of Homeopathy, Academy of Pathological Science. He had been a Fellow of the American College of Physicians since 1920.

ANNALS OF INTERNAL MEDICINE

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PRESIDENTIAL ADDRESS *

By JAMES D. BRUCE, M.D., F.A.C.P., *Ann Arbor, Michigan*

As I review my association with the American College of Physicians during the past year and during the twelve years I have been privileged to serve on the Board of Governors and later on the Board of Regents, I should be remiss in appreciation if I failed to pay tribute to the fine spirit that has characterized our Officials, the Boards of Regents and Governors, and indeed our entire membership. During my many years in practice I have always been associated with medical organizations and in none have I found more altruism, devotion and high purpose than in this College.

A notable achievement of the year just closing is the completion of the historical record of the College to 1940. While this may properly be included among the important events of the past year, attention should be called to the fact that this undertaking was begun under the presidency of Dr. Ernest B. Bradley and has been continued during intervening administrations. The history itself is a faithful record of College affairs and brings into proper perspective the ideals, purposes and personages that have made possible the College as we know it today. It is a masterly achievement and places us under deep obligation to Dr. William Gerry Morgan and his collaborators which we are glad at this time to acknowledge with appreciation and affection.

The American College of Physicians is devoted to the cause of internal medicine and is contributing in increasing degree to medical progress. It also is making noteworthy contributions through affiliation with other national bodies, particularly the central organization, the American Medical Association. The principal activities of the College are its Annual Meetings; the publication of the Annals of Internal Medicine; the maintenance of satisfactory standards of membership, which led to the organization of the Board of Internal Medicine; the encouragement of research; and, more recently, the promotion of postgraduate education.

* Address at the Annual Convocation of the American College of Physicians, Boston, April 23, 1941.

The Annual Meeting serves many purposes. It permits the renewal of friendships among our members, encourages an exchange of experiences in our professional progress and serves to acquaint us more intimately with the medical and social practices and traditions of the various centers visited. Probably greater than all these is the opportunity which these meetings afford the younger members to meet and know the older men who have made medical history, not only in this College but in American medicine. Indeed, I think it may be said that this last purpose justifies all the effort which these meetings entail, for they do require a long period of preparation which bears heavily upon our not too large staff at National Headquarters. In this program as well as in the routine conduct of the College, we are singularly fortunate in having as our Executive Secretary, Mr. Edward R. Loveland, who combines to a rare degree business and administrative ability with a fine understanding of our professional ideals. Indeed, if there be an "indispensable man," it is he.

The ANNALS OF INTERNAL MEDICINE reflects current scientific and social advances and serves as a permanent record of College progress. It is a publication of the highest order. This is due to the quality of the presentations and to the fine discrimination, good taste and scholarly attainments of our editors who have included, besides the present incumbent, Dr. Maurice Pincoffs, Dr. Carl V. Weller, and the late Drs. Frank Smithies and Aldred Scott Warthin.

The maintenance of satisfactory standards for membership in the College requires the organization of ways and means whereby the requirements for admission to membership may be met. Obviously, the College as now constituted cannot provide these opportunities, and it is extremely doubtful if it should ever attempt to do so. It must, however, foster resources now existing throughout the country to provide educational opportunities for graduates who aspire to the specialty of internal medicine and to the affiliated specialties.

Medical education has been divided, for convenience, into four phases: the pre-medical preparatory period, the undergraduate period which satisfies state and national legal requirements for practice, the graduate period and the postgraduate period. While each phase very properly may be clearly defined, it is altogether undesirable that they be dissociated. Indeed, the study of medicine should be thought of as a continuing process.

Among the different fields of medicine and at their varying levels the greatest need is for a related and orderly balance of educational opportunities. Nothing essentially new is required, no new machinery, but there should be a fuller comprehension of the health needs of society and a more equitable application of teaching and clinical facilities. That new and separate organizations were deemed necessary for different levels of professional training has been one obstacle to advancement in medical knowledge. Is it unfair to assume that the teacher who carries the student through to graduation

should continue to guide and direct the practitioner? Is the teacher in the postgraduate or graduate school on a higher level of professional and scientific knowledge than the teacher in a similar position in the medical school? No one would claim that he is. Oftentimes, he is the same man, teaching possibly in more restricted fields, but still the same teacher with the same attainments. If for no other reason than conservation of resources and practical economy, might not the medical school through necessary enlargement of staff and collaboration with all available resources undertake the whole medical teaching program, thus making a continuous process of what are now detached and more or less isolated efforts, particularly in the graduate and postgraduate fields?

The thesis is maintained by some that what is spoken of as "true graduate work" must actually be a detached and isolated process, free, so far as medicine is concerned, from such distracting interests as the care or even the consideration of disability and sickness. Graduate education, it is argued, must be confined to a purely theoretical atmosphere. This tendency to insist upon complete separation of the student from the patient and his problems and to ignore any association between the studies at hand and their possible application in clinical medicine, has the objective of "learning for itself alone." To those who have not adapted themselves to the exigencies of a troubled world, this detachment for a three to five-year graduate period and emergence with a Doctorate of Philosophy is alluring. Something may be said for this point of view. There may come much of peace with this devotion to a single task; a quiet pleasure in this very limitation. For some, a welcome refuge. The river no longer frets among the rocks of the strenuous undergraduate period. Nor is there the glory of the dashing waterfall—the adventure into the life work for which the graduate has been preparing himself—but instead the safe and steady flowing of the water through the sluiceway to a single wheel from which productive scholarship in pure and applied science may emerge.

But is this the goal? I think not. It is again but a beginning. Tomorrow, the graduate must take his place in the actualities of life, in practice, in teaching or in further research. But in all except the last he has been transplanted unless, perchance, in order to eke out a precarious existence during the graduate period he has served as a teaching fellow or assistant. Doubtless this would have been considered unfortunate, for if he entered into his teaching with any degree of enthusiasm he must, of necessity, have become to that degree detached from the isolation deemed necessary by the particular, or is it the peculiar, approach of the cloister-bound. Our graduate is unprepared for practice, and how may he ever enter into medical research if he is unfamiliar with the demands and problems of the sick room?

My reason for stressing this matter is to call attention to the effort of certain university graduate schools to assume direction of graduate education in medicine. I am not referring to graduate schools of medicine, nor am I questioning the necessity for the inclusion of subject matter beyond the

necessary clinical and scientific phases of graduate teaching, for we are all agreed that the broader the graduate student's cultural contacts and opportunities, the more likely is he to approach soundly the problems of medical practice. What I am questioning is the wisdom of permitting the direction of medical graduate work by those but remotely connected with the professional obligations of medicine. More particularly, I am pleading for a closer communion of the four phases of medical education as a continuing process: pre-medical preparation, the four-year undergraduate period, with its internship; the graduate period, with its hospital residency and necessary academic association, and the postgraduate period which contemplates study, teaching, practice and research throughout the life of the individual.

Our objectives, ideals and educational purposes have been clearly set forth by Dr. Irons in his discussion of the activities of the American Board of Internal Medicine as factors in scholarship in American medicine, and by Dr. Bortz in his presentation on the responsibility of the College in post-graduate training. The activities of our committees on education in the Board of Regents, under the chairmanship of Dr. Hugh J. Morgan, and in the Board of Governors, under the chairmanship of Dr. Edward L. Bortz, bid fair to justify the term *College* in its traditional sense as a positive factor in education.

The inclusion of general hospitals heretofore without university or medical school affiliation in the process of continuing education will contribute greatly to our present resources. The assumption of broader educational responsibilities on the part of a general hospital will not only enter importantly into a program of continuing education, but will also serve to raise the quality of medical service within the community. This, after all, is the final objective and criterion of all medical education. With the willingness to contribute to education which so many of our general hospitals have shown, together with the interest of medical faculties, I believe we will see affiliations between all forward-going general hospital staffs and our medical schools and universities in the not distant future. Dr. Sladen's presentation on our first day's program clearly indicates this trend.

While the College is following the ideals and purposes of its founders, practically all our activities have been modified to a greater or lesser degree by the needs of the nation in the program for National Defense. As the place which this country must occupy in the present conflict and the adjustments necessary have become more apparent, the medical profession is again called upon to make heavy sacrifice. It is with pride that we note the contributions of the College to the National Research Council and the Surgeons General through the Committee on Medicine and to the many other activities in the National Preparedness Program. Indeed, this national effort is occupying many of our members to the extent of preventing their participation in this annual meeting. If this preparation for defense so greatly occupies the profession in this country, to how much greater degree must it affect our Canadian friends and members who are engaged so valiantly, not

alone in preparation for defense, but in the activities of an armed conflict! To those among them who are fully occupied in this conflict for the preservation of individual liberty and world decency, as well as to those who have been able to slip away to the meeting of this College to which they have contributed so much, may I offer profound admiration, respect and affectionate greetings.

In a program for National Defense it is essential that all citizens contribute the services which they are capable of rendering with greatest effectiveness. Total war calls for total defense, but even in the presence of actual conflict it is important to promote the security of the civilian as well as to provide for the welfare of the soldier. There is considerable evidence that we have not been producing more graduates in the Health Fields than peacetime needs demand. If men are taken out of training for these professions, there is grave doubt that the future needs of the country will be adequately met. Students, interns, and residents, if inducted immediately into service, cannot make a contribution comparable to that which may be expected of them if they are permitted to continue their training to a satisfactory conclusion. This is not a plea for the exemption of students in the health fields, or in any field of education, but is simply to call attention to the desirability of permitting students to continue their work until they are qualified for effective service. The mistake must not be made of interrupting and disrupting the continuance of our present national patterns to the detriment of oncoming generations. Conscious as we are that there will be an inevitable backwash from the war in every phase of our national life, we should keep before us at all times the possibilities of softening these impacts through wise and careful planning.

In these strenuous times it is easy to see how matters of even considerable importance may be overlooked or dealt with inadequately. While I am reluctant to criticize, failure to comment in a field in which one has intimate knowledge, and particularly some responsibility, can scarcely be justified. As a member of the Committee on Medicine of the National Research Council, I feel it an obligation to call attention to the inadequacy of support on the part of the Federal Government in matters pertaining to the health and welfare of the armed forces. The Federal budget for 1940-41 carried an appropriation of only \$250,000 for the Health and Medical Committee. That this was wholly inadequate has been repeatedly called to the attention of the administration. Conservative estimates of the appropriation needed for the duties contemplated for 1941-42 range from a minimum of four million dollars to a maximum of ten million. I understand that the minimum figure of four million dollars has been requested. This sum would not be excessive if utilized in three fields alone—investigation in blood substitutes and more effective methods in transfusion, in the potentialities of chemotherapy, and in the general field of nutrition.

The importance of human conservation in both war and peace makes it mandatory that the agencies to whom this grave responsibility has been

assigned be not handicapped in their effort to provide preventive and curative measures. There can be no excuse for an administration that fails to provide all possible safeguards for the health and welfare of its people, both armed and civilian, while spending untold millions for mechanical and material preparedness, necessary as they are.

At this point I am proud to report that the Regents of the American College of Physicians appropriated \$10,000 for research necessary in the medical military field and that \$5,000 of that sum has been allocated by the Executive Committee on the recommendation of the Committee on Medicine of the National Research Council to the important research now being carried out at Harvard University on the possible use of bovine and human albumins as blood substitutes in transfusion. That no funds were available for the continuance and expansion of this vital work should be a matter for concern, not alone to the members of this College, but to all citizens loyally supporting an administration to which they have a right to look for the employment of every possible measure of safety for those from whom so much is being asked.

I am happy for this opportunity to congratulate those entering the College tonight. Although never a member of the Credentials Committee, on numerous occasions I have visited it. I wish I could convey to you how deeply I have been impressed with the meticulous consideration given by this Committee to the qualifications of every applicant. As you well know, certain scholastic requirements are essential, for these are something definite and in accordance with traditional educational measurements. If these were the sole criteria, however, neither you nor I could possibly have the pride in membership which is ours. Necessary as certain criteria of scholastic and professional accomplishment are, there is another qualification upon which little stress can be laid through the printed word, but which is a constant factor in evaluation for membership, and this is character.

In this period made dramatic by the utilization of mechanical devices in replacement of man power, it is essential to remember that, after all, man is the creator and master of the machine, and that the employment of inventions but increases the need for educated and trained workers. However, if initiative, devotion to ideals and love of fellow man, together with a reasonable sense of proportion, be lacking, much of this potential power brought to us by the inventive genius of man may serve merely to hasten our spiritual and material undoing. Guiding and directing all progress must ever be successive generations of trained men and women dedicated to that aristocracy of service which membership in the American College of Physicians contemplates.

MEDICAL ACTIVITIES OF THE AUGMENTED MILITARY FORCES *

By JAMES C. MAGEE, F.A.C.P., SURGEON GENERAL, U. S. ARMY,
Washington, D. C.

INTRODUCTION

In the course of my talk to you today I shall discuss the broad aspects of the task confronting the Medical Department in the expansion of medical facilities to provide for the hospitalization of the augmented military forces and for training of its own personnel. I ask you to bear constantly in mind that my discussion must, of necessity, deal with policies and doctrines enunciated in the Military Program of 1940-41 and covers Medical Department activities as they now exist and before the present "limited emergency" changes.

GENERAL CONSIDERATIONS

From the first phase of any expansion in the military forces, and throughout all subsequent military operations, organization must play an important part. The present trend toward mechanization emphasizes this axiom. The immense size of the forces which will fight wars of the future, owing to the participation of civilians, business and industrial elements as a part of the national war team, makes it obvious that a nation cannot hope to conduct a future war efficiently without most thorough *organization*. The ever increasing use of scientific weapons—mechanization of warfare—whether or not it reduces the size of actual combat forces, will more than ever call for thorough training if the combat force is to be reasonably effective at the outbreak of hostilities.

Military medicine has two main aspects—the professional or scientific and the administrative or organizational. Professional progress has turned upon two principal coefficients—the advancement of scientific surgery and the advancement of the science of communicable diseases. Medico-military administration has turned upon a single factor—the need of the nation for a well-organized professional army, however small, as a mechanism for its defense in time of need and as a nucleus from which emergency expansion may occur.

Under the Military Program of 1940-41, the strength of the United States Army will be 1,400,000 by July 1, 1941. Under this program the Medical Department is charged with providing an adequate medical service for the entire Army at posts, camps, and stations, within and without the continental United States. The means required to accomplish this task are those concerned chiefly with personnel, training, supply, and hospitalization.

* Read at the Boston meeting of the American College of Physicians April 24, 1941.

The chief function which the Medical Department must fulfill from the initial phase of any expansion is that of providing adequate facilities for sick and injured individuals. The stay of these individuals in hospital, whether of short or long duration, demands that such facilities as hospitals, supplies, and trained personnel be available and in efficient operation *from the very beginning of any military expansion*. This is a function quite dissimilar to that of the arms, such as infantry or artillery, since variable periods of training, short or long, will usually be available prior to their actual operations.

PLANNING AND TRAINING

Many complex problems having to do with either personnel or material demand advance study and solution if the sick and injured are to be efficiently and promptly cared for. Advance plans must provide for adequate and concomitant increases in personnel and for the dislocation of key personnel in existing installations to expanding units or installations if the necessary hospitals are to be available as augmentations in the Army occur.

The inherent obligations of the Medical Department include the added responsibilities of formulating plans for and providing training in the collection, evacuation, and hospitalization of the sick and wounded in war. This means that, in addition to training officers, nurses, enlisted men, etc., for duty in military hospitals, the Medical Department must train medical personnel for duty with the field forces. The validity of this statement is evidenced by the fact that, in every tactical operation in time of war, the Medical Department must execute a major withdrawal in its evacuation and hospitalization of casualties. The difficulties of this task and the need for special training for its execution may be realized when it is considered that this withdrawal of noneffectives must be accomplished against the urgent flow of troops and supplies for the great forward battle impulse.

The Medical Department has the distinction of being the only branch in the Army having a great series of units echeloned from the very front line itself back to the farthest end of the Zone of the Interior. This must be so in order that medical service may be continuously available and that sick and wounded may be moved methodically back to that echelon of medical service where the necessary facilities for the treatment of each type of case exist. The proper balance and distribution of medical personnel, units and installations in each tactical echelon are vital to success.

To accomplish its dual mission of providing facilities to care for the current sick and injured from a greatly augmented military force and of properly training its field component so that they may participate in tactical operations, when and if necessary, the Medical Department has been allocated 76 enlisted men per 1,000 of the total force. This totals 106,000. Fifty-two (52) enlisted men per 1,000, or 73,000, have actually been made available to the Department. Basic military and specialist training must be given before these individuals may assume their proper place in a highly

technical service. It has been necessary to employ qualified civilian technicians and specialists to supplement medical enlisted personnel in providing for the increased demands for hospitalization until our expanded training program might begin to bear fruit.

Predicated upon the fundamental doctrine that all training, commissioned and enlisted, in the Medical Department should be standardized, and upon the demonstrated results in the World War that organized instruction in camps and schools could be made to substitute to a certain extent for actual experience, the Medical Department has tremendously expanded its school facilities. This training must be in addition to the principal mission of providing an adequate and efficient medical service to approximately 70,000 hospital beds.

Briefly, the training program as it now is expanded will provide training as follows:

a. Medical Department Officers:

- | | |
|--|---------------|
| (1) Refresher Courses, Tactical Training-Medical Field Service School | 500 per month |
| (2) Refresher Courses, Hospital Administration (40 different courses in 6 different General Hospitals) | 300 per month |

b. Medical Department Enlisted Technicians:

- | | |
|---|----------------|
| (Dental, Pharmacy, Roentgen-Ray, Sanitary, Veterinary, Medical, Surgical, and Laboratory) (eight specialties in seven different Special Service Schools, in General Hospitals and the Medical Field Service School) | 1500 per month |
|---|----------------|

The planning, constructing, equipping and staffing, and actual opening of these Special Service Schools has been accomplished within a period of six months.

PERSONNEL

Since the present Military Program is one of training and not one of war, I have placed a rational limitation upon the number of physicians to be assigned with tactical units. This is evidenced by the fact that all professional units of the field forces are being activated with one-half enlisted and greatly reduced commissioned strength. As an example, numbered general hospitals (22) are being activated with 5 officers and 250 enlisted men, whereas these units at full strength require 73 officers, 120 nurses, and 500 enlisted men. It is felt that the five officers, with our present school program, will be sufficient to give this unit efficient training within one year. It is also felt that these units will provide the trained nucleus of enlisted personnel to activate our affiliated units, when and if it becomes necessary. This plan will result in a considerable saving in commissioned personnel with consequently less

disruption in civilian medical service. Plans are now in motion to establish an officers' candidate school to train individuals for commissions in the Medical Administrative Corps. Utilization of this Corps, whenever and wherever possible, will further reduce our requirements for strictly medical personnel.

With all possible economy in numbers, however, the present expansion will require approximately 9,000 medical officers. The present authorized strength of medical officers in the Regular Army is 1,230. The National Guard brought into service slightly less than 1,000 medical officers. This means that about 6,800 medical officers must be drawn from civilian and Reserve sources. All of the above figures are based upon a Military Program of 1,400,000 men in the Army.

The adequacy and efficiency of medical personnel is a matter of paramount importance to the Medical Department of the Army and to the medical profession of this country. Manifestly, the 1,230 medical officers of the Regular Army cannot render adequate and efficient medical service to approximately 70,000 hospital beds and, in addition, provide the necessary tactical training and administrative overhead to a military force of 1,400,000. The procurement and assignment of the necessary commissioned complement to duties best suited to them and of most value to the Army entail a task of great magnitude. The National Research Council and the several committees on medical preparedness are working in close coöperation with my office in providing information of inestimable value with reference to individual Reserve Officers' capabilities and experience.

HOSPITALIZATION

The present Military Program contemplates utilizing all existing military hospital facilities to a maximum. However, since the Army has expanded ten-fold and since many new posts, devoid of hospital facilities, have been established, the problem of making available adequate bed space, at the proper place and at the proper time, has assumed urgent importance. In general, 5 per cent of the military population represents the bed requirement in station or camp hospitals, and 1 per cent additional represents the general hospital requirement. Thus, of the total 84,000 beds required 70,000 are required in station or camp hospitals and 14,000 are required in general hospitals. Hospital construction, however, has been based upon 4 per cent beds in station and 1 per cent additional in general hospitals. Prior to the present expansion approximately 21,000 beds existed in military hospitals within the continental United States. This means that the Medical Department has had to plan, construct, staff, and equip military hospitals providing approximately 50,000 beds.

FINANCE AND SUPPLY

The construction of hospitals and the procurement of personnel in sufficient numbers and partially trained for duty in military hospitals and in tac-

tical units do not entirely fulfill the medical task. Military hospitals must, in addition, be given supplies, equipment, and utilities for operation. The Medical Department is charged with the responsibility of procuring and distributing all medical supplies for the Army. Medical equipment and supplies normally fall into two broad classes: those items used in the routine care of the sick and injured and those items known as field equipment. The materials of the first category are similar to those utilized in civilian medical and surgical practice; they are commercial in nature and their rate of consumption and maintenance requirements vary directly with the size of the Army. Field equipment and supplies, on the other hand, comprise those items and assemblies adapted primarily for emergency treatment and evacuation of battle casualties. These items are largely noncommercial in nature and their rate of consumption varies from a very small amount in peace time to astronomical proportions during actual combat operations.

The procurement and distribution of medical equipment and supplies, while controlled by my office, have been decentralized to medical depots where the actual purchases are made and the supplies stored and issued to using agencies. Prior to July 1941, the Medical Department will have approximately 70,000 hospital beds in slightly over 200 hospitals. All of these hospitals will be fully equipped from mess halls to operating rooms. This represents an expansion of about 350 per cent.

PROFESSIONAL

The Medical Department of the Army, during the expansion program, must maintain standards no less than those of the College of Physicians, which came into being to formulate and promote the highest professional ideals in the practice of medicine. Professional activities incident to the present program are primarily concerned with environmental sanitation, their supply, sewage disposal, anti-malarial work, venereal disease control, food and dairy sanitation, and efficient medical and surgical care. This is a small problem since, in all, there will be approximately 200 camps, posts, and stations with military populations ranging from 500 to more than 60,000. It must be manifest that the services of many agencies and many types of specialists will be required properly to perform these varied tasks.

The coöperation and active support of individuals and many civilian agencies are of paramount importance in the formulation of plans and in the execution of the heavy task laid upon the Medical Department. Several committees of the National Research Council are now functioning and rendering valuable aid to the Professional Service Division of my office. The Medical Department must have the support and coöperation of the profession in this nation if the type of medical service expected is to be rendered.

The Military Program of 1940-41 was designed as a training program, a preparation which the nation hopes will not only insure our peace but which will insure our being ready should the grave responsibilities of war come.

Except for battle casualties, the health and medical problems of the Medical Department will reach the same magnitude. The medical task is a distinct challenge to the medical profession of the United States. An understanding of the task and a sincerity of purpose in its successful accomplishment, augmented by the coöperation and active participation of the entire profession, will not only insure that our nation's armed forces shall receive the usual high standard of medical service but will inspire in the minds of all a high esteem for the medical profession of this country—an esteem which will be richly earned and honestly deserved.

to duties best

THE PROBLEM OF THE INTERNIST IN THE NAVY *

By ROSS T. McINTIRE, F.A.C.P., Medical Corps, U. S. N.,
The Surgeon General of the Navy

THE subject of this paper which I am presenting this afternoon, "The Problem of the Internist in the Navy," may seem a bit commonplace among such a distinguished group of internists as are the Fellows of this College. However, in view of the marked increase in the personnel of the Army and Navy, it occurred to me that it might be well for me to review something of the peculiarities of the duties that face the internists in the Navy, when to you who are in civil practice like situations would be very routine matters. Because many of you may be heads of departments in our large hospitals, should we come to a complete mobilization, I wish to bring up for your consideration a number of interesting conditions. Since they are being presented by one who is not an internist in the strictest sense of the word, please realize that they are being presented from the angle of the Military Surgeon.

Briefly, let me state that the functions of the Medical Department of the Navy can be classified as:

1. The maintenance of physical fitness among our entire personnel.
2. The proper physical selection of personnel.
3. The care of the sick and injured.
4. The elimination of the unfit by retirement and medical survey.

In the first group the internist plays a modest part. It is his duty to help find means to prevent disabilities, especially due to degenerative disease. In this rôle he is often called on to perform various types of research. The officer trained in public health and sanitation has a much wider field, finding and perfecting methods for the control of epidemic and infectious diseases. We in the Navy have a definite standard that every officer and man must be physically fit to perform his duties at all times, in all places, and under any conditions. A ship, to be 100 per cent efficient, must have a mentally and physically alert crew. Nothing disrupts organization on board ship more than men on the sick list. Take for example a gun crew on any of our ships: here we find team work in its highest state of efficiency. Every man is a specialist in his assigned task. The gun pointer spends many hours finding means to increase the speed with which he can get on his target. The gun captain works to find ways of correlating his group so that extra salvos may be put in the air. The training of this crew takes months. Should some of these men become frequent visitors to the sick list the efficiency of the whole is gone.

* Prepared for the Annual Session of the American College of Physicians, Symposium on Military Medicine, Boston, April 24, 1941.

In the second category the internist plays a very definite part, for here he must weed out the physically unfit before final acceptance. The well trained internist is of inestimable value in our Training Station organization.

It is needless for me to comment on the third group, as far as the duties of the internist are concerned. Here is his most active field. I will not say most useful, for it is difficult to decide where that margin really begins and ends. The problems that face the internist in the care of the sick are exactly the same as the problems that face you who are in civil practice. Because of this we constantly turn to you for aid and advice in helping to solve our problems. The Navy is especially grateful to the men who have helped to train our internists in the fields of cardiology, gastroenterology, and respiratory diseases.

I now come to the last group and this is the one where the problem of the internist in the Service and the internist in civil life diverge. When an officer or a man appears before a Board of Medical Survey to determine his fitness to continue on active duty in our Service, a number of problems present themselves:

1. Why is this man no longer fit to do active duty?
2. If he is no longer fit, then what part can he ever play in the Naval Service?
3. What disposition should the Navy make in this case?
4. How can he be properly rehabilitated so that he may find a useful spot outside the Service and secure as many years of life as possible?

One of the most distressing things that has come to our attention during the past 20 years is the apparent increase in coronary disease. We are making a study of the cardiac deaths that occurred in the Navy between the years of 1920 and 1930, and those that occurred between the years of 1930 and 1940. We are observing that the age incidence in these coronary deaths is lowering year by year. We also feel that the morbidity is much higher. Whether this is true or whether the diagnosis was missed in the earlier days is something we wish to discover. Are we crowding our officers to a point where the cardiovascular system can no longer care for its load? Are we piling on so much responsibility that the nervous system can not maintain its stability? These are problems that the internist must solve.

The management of a typical coronary case has a different aspect in the Naval Service. I grant freely that every coronary case that is properly handled should be able to assume some type of usefulness in the way of work. It is an absolute necessity that the individual be provided with some form of employment by which he can occupy his time. We have made a hard and fast rule among the officers that no one who has had a frank coronary attack can be returned to active duty. This may seem rather cruel and some of you may feel that we are wasting officer material by such a ruling. Consider then the responsibility that falls upon an officer, especially of the Line of the Navy. Speed is the essence of everything today. Our

ships go faster, our planes fly at increasing speeds. This means that the officer-in-command of Units, or a single Unit, must have all his faculties alert at all times. I can leave to your imagination what would happen to a number of ships in column, traveling at a speed of thirty knots, should the Commander of this Division, or the Commanding Officer of a single ship, collapse at his station on the bridge at the time the command was passed to change the course of the formation. It is for this reason that we can not allow an officer who has had one serious heart attack to assume these spots of great responsibility.

The cardiovascular case presents very much the same picture. How much stress and strain should we allow the individual who has a damaged vascular system, or who is carrying a very high diastolic pressure? How long should we permit this man to go before we call a halt and return him to civil life where he can be rehabilitated in a normal fashion?

The next group that gives the internist a great deal of cause for worry is the ulcer case. A peptic, or a duodenal, ulcer is always a rather difficult case to handle, unless the individual can be hospitalized. Consider then the difficulty the medical officer of a ship has in attempting to care for a definite case of duodenal ulcer, when the diet field is so thoroughly limited. Life on board ship is certainly not conducive to ulcer repair. The internist is called on to make the decision in these ulcer cases as to where the safety point lies, as far as the patient is concerned, and as to when he no longer can carry on his duties at sea. This means separation from the active list of the Service.

Of course, we have many other conditions that give a great deal of cause for serious thought. The field of the tuberculous individual is one of the most important. In passing, I may say that we are roentgen-raying the chests of all men entering the Naval Service. Upon their discharge the same will be done. This I am sure you will agree is a step in the right direction in aiding to weed out the tuberculous individual. It also protects the Government against many claims that might be without foundation, as was seen during World War times.

In the consideration of serious diseases, such as those due to endocrine imbalance, the question is always before the internist as to the proper means for carrying this individual along so that he may perform his duty efficiently. In some conditions, such as hypothyroidism, diabetes, or certain heart disorders that require, from time to time, digitalis, quinidine, or other special drugs, the proposition of always having the proper remedy on hand to make the individual efficient markedly lowers his usefulness to the Service. In other words, a man who has to depend upon a bottle of medicine for his efficiency can not be considered a top flight officer. Still this individual in civil life can be carried on for many years in a reasonable state of health and can pursue his profession, or trade, with very little time on the sick list.

One subject that is coming in for a great deal of discussion these days is who should treat the various forms of syphilis. The Navy has been criticized in the past for putting these cases in the genito-urinary Service. We

are told that syphilis is a medical condition. Quite true it is. I think it is very possible that our medical services could easily care for the active luetic infection. There is a definite doubt in my mind as to the propriety of the internist treating the neurosyphilitic case. I am making no attempt today to pass a final word on this subject. I think it is one that is open to argument and we, in the Service, will be interested in receiving constructive recommendations. One of the most troublesome groups with which we have to deal is the luetic of long standing, or those cases in older age groups, when all efforts to find the focal point of infection are negative, and history avails nothing.

This brings up the subject of "Line of Duty" which is one of the most important that faces every officer and man when he enters upon the sick list. His retired pay or pension will depend upon his ability to establish his line of duty status. The doctor must serve in this additional regard. He must fairly judge his cases and see that no injustices are done and that no means are overlooked to aid the patients in clearing up delicate points which may mean everything to them in the future.

The mental misfits have long been a constant source of worry to our Service. We are planning to relieve the internist from this duty of attempting to segregate these unfortunates by having well trained psychiatrists and a few good psychologists attached to every Training Station.

You may now ask what we are going to do with the officers or men of years of service who have great ability and experience. Are their services to be completely thrown away and of no longer use to the Navy? So far as the active list is concerned, the answer is "Yes." In times of emergency, however, such as the one we are now in, we have adopted a system which is not unlike yours in civil life. We are recommending many of these old heart cases, and a certain number of the hypertensives, for spot jobs. By spot jobs I mean carefully selected duties where a man can give the Service the benefit of his experience in his specialty, without subjecting him to the stress and strain of high responsibility. We are also able to do this in a like manner with many of our retired enlisted personnel. We are attempting, however, not to order back to duty any retired officer or man whose disability is of such an extent or character that his return would light up his old condition and possibly bring about his death. At a time like this, of course, the nation and the Navy have the first call on Service personnel, whether active or retired, but one should never lose sight of the fact that the officer or man who has had long and honorable service should receive consideration. Surely we, as doctors, must consider the dependents of these men.

The internist in the Navy is given every opportunity as he goes along to increase his professional efficiency by postgraduate work in our civil institutions. It is the policy of the Bureau of Medicine and Surgery to be sure our internists attend as many of the clinics throughout this country as it is physically possible for them to do.

We are making every effort to open up research in many lines where we have the facilities and the experience with which to carry them out. As you know, the Navy has done a great deal in the study of the effect of oxygen and helium in diving. We are now turning this vast knowledge to the higher altitudes. We find that we have bridged a great gap by this experimental work under high pressures and with the coöperation of many of our men in institutions in civil life, we hope to add a great deal to what a human being can do above the 35,000 foot level.

The field of industrial medicine is not being neglected. Here again we are turning to civilian institutions for help in training more personnel for use in our industrial plants.

In this short review I have merely attempted to give you an idea of what the internist in the Navy must do in addition to treating his cases. I do this realizing that in case of a complete mobilization many of you, who are not now in the Medical Reserve Corps of the Army or the Navy, will probably wish to join. He who may come into our Service will find himself assigned to a department, where his specialty will make him extremely useful. I can promise you an interesting and busy service which I am sure none of you will ever regret. To you who may have your eyes on the horizon, we have our Mobile Hospitals which will be located on our far-flung islands. There the problems of the various tropical diseases will confront you. Or perhaps you might prefer duty on some of our Hospital Ships. In any case, let me assure you that life will never be dull. The Navy will be very glad to have the opportunity of your coöperation and active participation.

MEDICINE IN ENGLAND NOW *

By THOMAS PARRAN, F.A.C.P., SURGEON GENERAL, U. S. PUBLIC HEALTH SERVICE, *Washington, D. C.*

MODERN science has extended the area and scope of medical defense against enemy action no less than it has extended the area and scope of war operations. The whole population of Great Britain is in the battle line. The whole medical profession is in the forefront of the battle. As a member of a Commission on Civil Defense, I spent the month of February in Great Britain. This commission was appointed by the Council of National Defense at the request of the General Staff of the Army. Military science has evolved through the centuries, engaging some of the best minds in every country in every age. In Great Britain during the past few years, there has been developed a new science of civil defense just as intricate, just as complicated in its organization and operation as military science. Yet there have been few guide posts, no trained personnel. It is commonly agreed that the system, especially in its medical aspects, accomplishes its purpose effectively, through an integration of governmental, professional and voluntary effort.

In planning civil defenses, the British made two major mistakes: 1. They assumed widespread and intensive raids immediately at the outset of the war with as many as 30,000 casualties a day needing hospital care. 2. They did not envision prolonged continuous night bombing necessitating the use of shelters as sleeping quarters.

To care for the expected casualties, they doubled the prewar complement of hospital beds throughout the country; by discharging convalescent patients; by evacuating mental hospitals, institutions for the feeble-minded, the aged, etc.; by constructing huts,—temporary wards frequently on the grounds of an existing hospital; by converting large estates into hospitals; and by “upgrading” existing institutions through the addition of operating theaters, the provision of nursing and surgical staffs, etc.

In preparation for war, the country was divided into 12 regions with a regional commissioner in charge and with representatives of each Ministry assigned to the commissioner. This decentralization provides independent self-governing areas in the event of invasion, or other enemy action which would disrupt communications. The public health, hospital and medical services are a part of the regional plan.

The war has brought large responsibilities to the Ministry of Health and to local health authorities. Under the Ministry, an Emergency Medical Service was organized. An important first step was a cataloguing of all hospitals in the country, voluntary and public. The use to which each should be put was decided.

* Read at the Boston meeting of the American College of Physicians, April 24, 1941.

The London area was recognized as a special case and its emergency hospital service was based upon ten sectors radiating fan-like from the center outward and extending well beyond the metropolitan area. In each sector the hospitals are classified into Casualty Clearing Hospitals, Advance Base Hospitals, and Base Hospitals, and additional beds provided for each.

The Casualty Clearing Hospitals are near the center of London and other large cities. A large proportion of regular patients were evacuated, especially from the top floors and glass cubicles. In addition a specified number of beds in each are kept vacant for casualties.

The Advance Base Hospitals usually are located 15 to 30 miles from the center of the city. The average capacity is 1,000 to 2,000 beds. Patients are admitted to these hospitals from the Casualty Clearing Hospitals or occasionally directly from first aid posts.

Base Hospitals are located 60 to 100 miles out, and have 1,000 to 3,000 beds. Patients admitted to these have been classified into specialty groups, —orthopedic, maxillo-facial, neurosurgical, eye, etc.

The Emergency Medical Service pays the voluntary hospitals £3 per week per bed reserved for casualties. When occupied, the rate is £4 per week. Due to the lack of casualties, this has proved a boon to the voluntary hospital budgets.

It should be emphasized that there is in Great Britain now essentially one integrated national hospital service for civilian and military casualties. There are no separate base hospitals for the Army. Since this whole system has been scrambled together, the British doubt that it ever will be completely unscrambled.

The first-aid posts were organized by the municipal or county health authorities under standards proposed by the Ministry. In general the cost of ambulances and of the whole air-raid precaution service is reimbursed by the central government. To train the first-aid teams has been a major task. The need for additional nurses has been met by training more than 120,000 nursing aids and auxiliaries.

While total war creates a demand for many skills, the skill in which there is the greatest shortage is that of the doctor. Four days ago, the President responded to the urgent request of the British Red Cross for American doctors. He said: "To any American doctor who is eligible and able to do service, this cause presents a splendid opportunity." Assurance that medical aid is promptly available to all casualties is an important consideration in maintaining morale. Day and night in every operating theater, a surgical team stands by. A doctor is on call or working in every first-aid post. Each night a doctor visits all large shelters. Moreover a modern army requires many doctors, especially in mobile mechanized warfare. Doctors are needed too in the large factories and to supply the needs of an expanded Navy and Air Corps. Up to now epidemics have been held in check. Air raid casualties have been fewer than anticipated and have received prompt

attention. To accomplish these results, however, the British doctors have been under a severe strain and medical services for the general population have been diluted. Britain's appeal to the American Red Cross for at least 1,000 of our young doctors is a great opportunity for us to meet a real need. Aside from its humane aspects, American doctors, working side by side with British surgeons and physicians, will acquire valuable experience in the medical technic of modern warfare. Those who answer this Red Cross appeal will not only have rare professional opportunities but will also have the satisfaction of giving help where it is sorely needed. I feel certain America's doctors will answer this call. The needs are great, the rewards will be greater.

The British have been very intelligent in using their medical resources to the best advantage. No medical or dental student is allowed to volunteer and he is not drafted if he passes his examinations from term to term in an accredited school. This deferment is not a "hiding hole" for slackers. Every such student upon graduation or after one or two 6-month periods of internship is automatically called to service for the duration.

When the system of the Emergency Medical Service hospitals was established, they were staffed by doctors of all ages who were, in effect, requisitioned from civil practice. In London, for example, the staffs of the teaching hospitals located near the center of the city were dispersed to the peripheral hospitals. The regional, sector, and group hospital officers who themselves had been drawn largely from the staffs of voluntary hospitals, decided who would go to the peripheral base hospitals and who would stay at home. With rare exceptions the assignments were considered as orders. For example, a large proportion of the specialists in Harley Street with expensive practices and equally expensive offices and other commitments, were recruited for full-time service at a standard pay of £800 per year. They abandoned their practices, moved 50 to 100 miles to a base hospital and stood by waiting for patients. No casualties appeared during the early months of the war. Naturally some of them drifted back to their accustomed practice. Recognizing the situation, the Emergency Medical Service gave these doctors the choice of continuing on a full-time basis or of rendering a part-time service; subject to call at a lower pay (£300 per year), but with the understanding that if enemy action increased and the government required their services full-time, such services would be given at the same part-time rate. Most of the doctors accepted the offers, leaving skeleton staffs, mostly junior men, at the peripheral hospitals. When the heavy blitz started in September 1940, the full-time service of additional doctors was required in the peripheral hospitals and the financial arrangement was readjusted.

Prior to the war there was perfected a medical war organization for the country. At the head was a Central Medical War Committee, composed of the leading physicians, members of the British Medical Association. The Secretary of the Committee is the Secretary of the British Medical Associa-

tion. To this committee was given the task of registering every doctor and every medical student in the country.

Whenever the military forces requisitioned a quota of doctors, the Central Medical War Committee allocated the quota to the various communities in Great Britain in proportion to the number of doctors still remaining as related to the population. When the quota is sent to the civil subdivision (county, city, etc.) a local medical war committee, made up of senior doctors, selects the persons who can most easily be spared from present tasks. Doctors in health departments and in important hospital positions are not disturbed. Younger doctors are given preference for service. When a doctor is selected by the local medical war committee he responds in nine cases out of ten. The exceptional doctor may ask for deferment because of some determining personal consideration. His appeal is reviewed. If the decision is not in his favor, he has the right of appeal officially to the Central War Committee in London. Ordinarily, financial considerations are given scant attention.

If we are to learn anything from the British experience on the medical front, we must reorganize our approach to the problem of medicine's contribution to the defense effort. The medical needs of the civilian population should be considered in all recruitment plans, and should be balanced against the military needs. The Health and Medical Committee, Council of National Defense, or a comparable group should be given responsibility for broad national planning. Medical personnel for military, industrial and civilian health and medical services should be recruited on a quota basis, having in mind the service which each individual physician can render best. Volunteers should not be accepted if they are doing a more essential civilian job. The objective should be to see that each doctor is doing the task for which he is best fitted.

Under a national medical committee, there should be similar committees on medical personnel in each State and in each of the larger communities. These State and local committees made up of senior doctors should decide who should join the services and who should remain at home.

All medical and dental students enrolled, all students accepted for admission and those completing their courses satisfactorily in accredited medical and dental schools should not be drafted until graduation and the completion of an internship, after which those who are physically fit should be required to render a period of service to the government.

The successful local organization of medical defense efforts in Great Britain was possible because for two decades or more, Britain has had a nucleus of trained medical officers of health. Without this nucleus, effective local medical defenses could not have been organized. We should take steps promptly to double the number of doctors with training and experience in public health and medical administration. In addition, there should be a comparable increase in public health nurses, sanitary engineers,

sanitary inspectors, laboratory technicians and other technical public health personnel. New training centers will be needed for the training of key persons who in turn will train others who will work under supervision in local communities.

Central planning for medical aspects of civil defense should be done. This should include the survey of existing hospital facilities, area by area, and of those structures which can be converted to hospital use. Estimates should be made as to additional hospital beds needed, area by area. The number and location of the beds will depend upon the position of the area in reference to vulnerability to enemy action.

This is not the occasion for a comprehensive outline of all needed steps. Nevertheless, we should make our plans now, on a national scale. There is no time for planning when the enemy strikes. Among other things our plans should include provision of additional operating theaters and their protection against enemy action; the protection of existing hospitals; the consideration of safety from air attack in new hospital construction, the number, location and equipment of first-aid posts, the provision of ambulances of a standard type with standard fittings, and the earmarking of commercial vehicles for emergency ambulance service, the planning of decontamination centers and training of key personnel in each vulnerable area in anti-gas warfare. I am not recommending all of the above for the whole country but for those areas designated by competent military authorities as vulnerable to enemy action. In addition, special mobile staffs trained in medical defense measures should be available to aid in the organization of such civil defense measures in our Territories and possessions and in those areas which we are committed to defend.

It should be emphasized that in the midst of war, the British have not curtailed but have extended their social insurance and other social laws, and have adapted them to war needs.

Finally, let me say that we doctors in the United States should be inspired by the example of our British medical colleagues. In the midst of war they are planning for the peace. The British Medical Association has set up a Medical Planning Commission to "study war-time developments and their effects on the country's medical services, both present and future." In an editorial comment the British Medical Journal points out that the war has thrown into sharp relief the deficiencies of their peace-time system of administering relief to the sick and of promoting and maintaining the health of the people. "The British Medical Association now proposes to prepare for the return of peace so that medicine may be ready to meet its responsibilities in a world in which many values will be changed, fresh conceptions of society will be formed, and in which new stresses and strains will appear in the moral, material, and economic fabric of the democracy we hold to be our rightful heritage."

I have every confidence that medicine in America will meet whatever demands the future may impose, whether of war or of peace.

NUTRITION IN THE UNITED STATES: A PROGRAM FOR THE PRESENT EMERGENCY AND THE FUTURE *

By RUSSELL M. WILDER, M.D., F.A.C.P., *Rochester, Minnesota*

THAT the present emergency calls for a great increase in the size of our Army and Navy with provision of all that is necessary to make these armed forces into a superlative instrument of war, scarcely anyone denies. That it calls for rapid acceleration of those of our industries which can engage in the manufacture of materials of war, everyone will grant. That to accomplish what needs to be done will entail sacrifice on the part of almost everyone, and longer and more arduous work for many, will be acknowledged. These are self-evident truths. On them, however, is based my concern, and that of every thoughtful student of nutrition, with the existing degree of malnutrition, because controlled experimentation has taught us that willingness to sacrifice and to work, as well as the determination and courage, necessary not only in the Army but in those behind the lines, are human qualities that weaken when foods fail to provide what is needed for satisfactory nutrition.

That many American diets are deficient in quality, deficient especially in those chemical catalysts, the vitamins, which activate human energies as spark plugs activate machines, is a conclusion based on highly qualified medical advice, that of Drs. Jolliffe, McLester, Spies, Sydenstricker, Tisdall, and many other physicians who, because of large experience with deficiency disease, possess the rather special training necessary to recognize the widespread prevalence of submarginal degrees of deficiency disease. It is based also on many recent nutritional surveys including the extensive governmental studies of consumer purchases conducted by the Bureau of Labor Statistics, the Bureau of Home Economics, and the National Resources Committee.

The English, faced with a very similar problem, are taking vigorous steps to combat it. Dr. Geoffrey Bourne has written of this in his book, "Nutrition and War." That millions of people should live on or below the borderline of minimum nutrition is a special danger in time of war. Such persons not only are unable to work effectively, but also they succumb easily to infectious diseases and offer a breeding ground for such pandemics as the influenza of World War I.

The necessity for action on the nutrition front is no less pressing than that for mobilizing physical equipment, and the time element is equally im-

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portant. It will take months and even years to gear up the industrial facilities for making the required tanks, planes and ships. It will require as many months or years to gear up the manpower of the nation to run the accelerated machinery. Fortunately, through the foresight of the head of the Consumer Division of the National Defense Advisory Commission, an early start was made. The leadership now is provided by Governor McNutt, Director M. L. Wilson, and Surgeon General Parran. The scientific guidance is in the hands of the nutritional experts, in government and out, of the Committee on Food and Nutrition of the National Research Council. This campaign soon will be intensified. It must have the fullest possible support or the consequences may be disastrous. Without strong human defenses, military defenses fail.

THE NEED FOR BETTER NUTRITION NOT LIMITED TO THIS EMERGENCY

One permanent good at least seems likely to emerge from the present defense activities. The recognition which nutritional science must now receive comes none too soon. Entirely apart from the present emergency, the nutritional situation is a cause for grave concern. It presents, indeed, a public health problem of major importance. One sometimes hears men say, however, that our food habits are no worse than they were before we ever heard of vitamins; no worse, these persons say, than during the first World War, which we fought effectively.

Actually our food ways for some 60 years have been worse than at any previous time in history. They are worse today than they were in 1914, for the reason that more years have passed since certain detrimental changes were made, some 60 years ago, in the food habits of our population.

Those who have had training in biology appreciate that changes in nutritional environment are badly borne by all organisms from bacteria to mammals. A changed nutritional environment in the case of vertebrates and other higher animals means changes in the constituents of blood and lymph; in other words, changes in the "milieu interne," so called by Claude Bernard. Adjustments to changes of the milieu interne are difficult. We adjust better to external temperatures, for instance, than to equal alterations of the temperatures within the body. We can immerse our bodies in the ocean, but would perish promptly if our blood contained as much salt as ocean water.

Adjustments to changes in the blood and lymph are possible, but require generations for their accomplishment. I have no doubt that given several thousand years the human race might learn to live efficiently on a third or a fourth the amount of thiamine (vitamin B₁) which its ancestors got and came to depend on. Also, the human race might learn to do without ascorbic acid (vitamin C), as rats apparently have learned to do. But in the learning countless individuals would be sacrificed and for a long period succeeding generations would deteriorate.

A changed nutritional environment of major degree is intolerable. One of a minor degree may be appreciated with difficulty and make itself felt only from one generation to the next. This is readily shown with laboratory animals. It is more difficult to trace in the case of human beings. Although not established by sufficient proof, there is reason to believe that a relationship exists between the increasing incidences of several of the so-called degenerative diseases and the great change in our food ways which, as I have said, occurred about 1880. I have in mind arteriosclerosis, diabetes, some forms of arthritis, and some insanities.

You will be wondering now about this change in food ways, and for more details I must refer you to the fascinating book "The American and His Food" by Professor Richard O. Cummings. Of major significance was the introduction of modern methods for milling wheat and refining sugar. We did to wheat what the Chinese did to rice, i.e., milled out of it and discarded or fed to swine and cattle much of the good in it. Even worse than this we replaced about half the wheat our ancestors ate with refined sugar, than which there probably is no food less satisfactory from the standpoint of nutrition. In consequence the average American diet of today, even in families with liberal money expenditures for food, contains only about a third as much thiamine as in Civil War times. And with the thiamine has gone a quota of many other nutritional substances, other vitamins and minerals. The nutritional loss from this replacement of the undermilled flour of the past with white flour and sugar has been compensated for, to a certain extent, by a greater consumption of garden vegetables and milk. Unfortunately neither garden vegetables nor milk provide thiamine as generously as does wheat. They are poorer, perhaps, in some of the other vitamins and minerals found in wheat. They also are more costly, at least for the city dweller, and so have gone mostly to families in upper income groups, leaving grave vitamin starvation among our poorer families.

In a nutrition laboratory at the Mayo Clinic, Dr. Williams, with Dr. Mason and other associates, has been studying volunteer subjects who are given diets made adequate in all respects except in thiamine. The scientific control is rigid. The food is analyzed for thiamine by Dr. Mason, and a double check is obtained by periodic analyses of excretions. The allowance of thiamine is regulated and changes in dosage are made without the knowledge of the subjects. In the course of such induced thiamine deficiency studies we have frequently seen cheerful, happy, vigorous, industrious young women become morose, depressed, fearful, irritable, uncoöperative and slovenly in personal appearance. They lack the strength to work and any interest in working. It is equally phenomenal to see these same young women return to their normal selves when the intake of thiamine again is raised to an adequate level, but the longer the deficiency continues the more difficult it is to restore these subjects. From this, one wonders whether continued deficiency of the thiamine content of American diets may not have led to a certain degree of irremediable deterioration.

Physicians until lately have been thinking of nutrition too much in terms of *frank deficiency disease*. A few persons die of *beriberi* in this country, but even before it was learned that nicotinic acid could be curative in pellagra, the number of deaths from pellagra recorded in any single year did not exceed a few thousand. The milder degrees of nutritional deficiency are the nub of the nutritional problem. Williams' experiments at the Mayo Clinic show that a man can subsist on as little as 0.6 mg. of thiamine a day, but that with this small intake he is only half alive. To function efficiently, to do the things that must be done now, he needs at least twice this amount, and for a safety factor at least 2 mg. How many men get 2 mg. of thiamine a day? Not more than half, probably fewer than a third, of the adult male population of the country.

Using sugar in the amounts we use it, and depending on plain white flour as we have done, thiamine, nicotinic acid and riboflavin are among the vitamins most likely to be inadequately represented in American diets. That is the reason for the recommendation of the Committee on Food and Nutrition of the National Research Council for putting these particular vitamins into enriched flour and enriched bread; that, as well as the fact that these three vitamins are involved in the oxidative changes whereby energy in the body is released from sugar. The more starch the diet contains, the greater the need for thiamine, nicotinic acid and riboflavin.

I may have emphasized disproportionately the deleterious effects of the introduction of white flour and refined sugar. Other serious faults exist in American diets. In some regions of the United States, and by some families everywhere, too little protein is obtained. In many of our poorer families lard is used instead of butter, and in their diets vitamin A is frequently wanting. In other diets, fruits are lacking and vitamin C is missed. In many diets, calcium is lacking in adequate amounts. It is difficult to get enough calcium without drinking milk, and many people don't like milk.

PLANNING FOR BETTER NUTRITION

What then needs most to be done? The problem involves economics, but economics cannot be changed rapidly. Half of the people in this country have less than 25 cents a day to spend for food, but even if the average income of the economically lower half of the population could be doubled, an amount of malnutrition, because of bad food habits, would still remain. Food habits are correctable, but to change them requires years of patient endeavor. Education will help much. The present nutritional program contemplates extensive use of education and this must be extended as much as possible. However, the learning capacity of many people is limited. The amount of training given the average citizen cannot well extend beyond teaching him appreciation of the nutritive values of vegetables, fruits, meats and dairy products. In the country the success of education will be greater, because many of these so-called protective foods can be grown in the garden,

and poultry and milk can be had economically. In the cities, unfortunately, the protective foods are beyond the means of many families or unattainable in sufficient quantities.

The educational program also encounters the obstacle that most people do not care to think too much about their choice of foods. I have frequently noted that even nutritional scientists pay little heed to what they eat; indeed, I must confess to some shortcomings in this respect myself.

Professor J. C. Drummond of London University has protested against the shibboleth that nutritional security can be found in what is vaguely called a mixed diet—that in such a diet one food can be depended on to compensate for the inadequacies of another. There is no such security today for the reason that more than two-thirds of the calories of diets come in the form of sugar, plain white flour, and processed fats. In such circumstances it is almost hopeless to expect the remaining third of the calories to carry all that is required of vitamins and minerals. Dr. Lydia Roberts frequently has made this comment.

IMPROVING STAPLE FOODS

What needs to be done if we are to have good diets everywhere is to make every food carry an appropriate share of some part of the responsibility for an adequate daily supply of all the nutritive essentials. Could that be done people would find themselves always surrounded by protective foods and in such favorable surroundings a mixed diet *would* provide security.

Alternatives to such a procedure can be thought of. We could try, for instance, to provide everyone with vitamins in capsules or tablets, or as has been suggested, with a supplementary food composed of wheat germ, dried yeast and other vitamin concentrates. The objection to these alternatives is psychologic. Most people don't like taking medicine and won't take capsules or tablets, at any rate not for long. The vitamin capsule, even if it could be compounded to provide all that was needed, which is a doubtful possibility, would be neglected. The supplementary food would encounter consumer resistance. People are as choosy with their breakfast cereals as with their brands of cigarettes, and to concoct a supplementary food to suit the taste of everybody presents a practical impossibility. Vitamin capsules and supplementary highly fortified foods have a place of importance in restricted fields, but much more likely to succeed in any nationwide attack on malnutrition is a program based on assuring the nutritive quality of all foods, with special attention to the inexpensive staples.

There are two ways to accomplish improvement of staple foods. Perhaps in time people can be persuaded to eat only natural foods, unprocessed food. The idea dates from Sylvester Graham. However, the virtues of natural foods have been extolled for a hundred years since Graham's time and the results are disappointing. Much good has come from nutritional education, but far from enough to solve the national need for better food.

Legislative prohibition of processed foods also probably would fail. Such a procedure is not the democratic way, and the net result would be a return of the bootlegger. Also the vested interests aroused would be gargantuan, and in practice any such procedure would create enormous difficulties of transportation and distribution. The costs of food would rise. The natural foods are perishable and perforce expensive.

Fortunately another way exists, one that will not conflict with popular tastes or seriously disturb investments of industry in plants and equipment, a way by which the advantages of food processing may be retained and disadvantages corrected. The food processor until recently has devoted his attention to securing a product pleasing to eye and taste. He has not been concerned with nutritive values. He knew little or nothing about such values, but he now is ready to learn and is prepared to act.

ENRICHING FLOUR AND BREAD

A start already has been made with flour and bread. Plain white flours and plain white breads are being enriched with thiamine, nicotinic acid, riboflavin and iron, according to the recommendations of the Committee on Food and Nutrition of the National Research Council. As the other factors of the vitamin B complex become available inexpensively, they too may be included in the specifications for these products, and as methods of milling develop which permit retaining the vitamins and minerals in white or creamy flours, their use will provide not only thiamine, nicotinic acid, riboflavin and iron, but the other nutritive constituents found in wheat. The reason for the emphasis on content of thiamine, nicotinic acid and riboflavin is the knowledge we now possess that these three vitamins are specifically concerned in the oxidative reactions in the body by means of which we liberate the energy in the sugar that comes from starchy foods like flour.

The reason for the emphasis on having a white or at most a creamy colored flour is that most persons don't like brown bread and those who eat brown bread do not, as a rule, use whole wheat flour in their cakes and pastries or in their gravies and sauces. To get the vitamins needed for the effective utilization of the starch of flour, not only flour used in bread but flour used for all purposes should contain them.

Furthermore, the brown bread that most brown bread eaters buy is made of part white flour and is only partly graham. The brown bread eaters recall the cold bath takers. The benefit they get impresses me as being mostly a feeling of righteousness. Also, as physicians we know from much clinical experience that bran flakes are not well tolerated by many persons. Brown and gray breads won't do for such persons. They are disliked by others, and for these reasons the dark loaf cannot be expected to compete successfully with the white where both brown and white loaves are available.

What little opposition thus far has come to the recommended program for enriching flour and bread is mostly from those who hold as a matter of

principle that "the good is really the enemy of the best." Most of us believe it is "better to make this compromise than to let the people suffer from vitamin starvation, perhaps for years." *

EDIBLE FATS SHOULD BE IMPROVED

Edible fats must soon receive attention. Just as products of wheat supplied mankind for untold generations with the water soluble vitamins of the B complex, so butter, cream and organ meats like liver and bone marrow provided him with much of what he needed of the fat soluble vitamins, especially vitamin A and vitamin D. Less recently than in the case of wheat a change took place in this arrangement. Milk production became an industry, and cows fed on winter fodder yield milk with butter fat less rich in vitamins. Also, in place of butter margarine was developed. At first it was made of fats of animal origin, later to a large extent from vegetable oils. In neither of these products does the content of vitamin A approach that of butter. Vitamin A can be synthesized in the human organism, as in the cow's, from carotene, and plenty of greens in the diet in most cases will provide what carotene is needed. Greens, however, are expensive for city dwellers, and infants and very young children cannot well take greens or do not do so. The story of how Danish children lost their eyes during the last war because the Danes, tempted by high prices, sold their butter to the Germans has been frequently recounted. Since then fortification of margarine with vitamins A and D has been made compulsory in Denmark by legislation.

Last year in the United States not more than 100 million of the 400 million pounds of margarine were fortified, and by regulation no margarine containing any animal fat could be thus improved. That regulation now, by an order of the chief of the Bureau of Animal Industry, has been suspended. It seems to me probable that we shall go further than this. We certainly must recommend that butter and margarine which contain an approved amount of vitamin A and vitamin D be preferred to other butter or margarine, but also because many persons use lard as a substitute for butter I would like to see all lard with a fixed added content of these vitamins. The expense would be insignificant. The benefit among the poor would be enormous. The prevalence of night blindness in England is said to be revealed by an increasing number of "blackout" accidents and deaths.

THE MILK PROBLEM

Improving staple foods need not, and indeed should not, be limited to additions of vitamin concentrates or synthetics. The distribution of milk as this now is practiced is wasteful. Much of the production is never brought to the market, and many who need milk most cannot afford to get it. Remove the fat from a quart of whole milk costing the consumer ten

* The quotation is from the answer by Bruce Bliven to a letter in the Countryman, England (New Republic, March 24, 1941, p. 407).

cents or more, sell it as butter or cream to those who can afford to buy butter and cream, and in the skim milk solids that remain you have another product which being more or less imperishable could be distributed for a cent or two, a tenth the cost of fluid milk. Of all the valuable nutritives contained in milk, by far the greater number remain in the skim milk solids. In this sense skim milk solids represent the best part of milk. They are a good food source of calcium, and more diets probably are deficient in calcium than in any other food essential. Also in milk and remaining in the skim milk solids are all of the water soluble vitamins and the most perfect proteins known, casein and lactalbumin.

But how can universal use of skim milk solids be obtained? This problem now is receiving attention in the nutritional program. At present much skim milk is wasted or used uneconomically in feed for swine and poultry. A solution I have to propose would provide an answer not only to this problem, but to another, that of sugar.

THE SUGAR PROBLEM

The daily consumption of sugar in the United States, most of it refined sugar, averages per capita approximately five and one-half ounces. The addition to the diet of this material, representing more than 600 calories, or a fourth of all the calories of the diet, and carrying no vitamins and no minerals, is a major nutritional error. Nutritionists agree that of all foods, sugar unquestionably is the worst. Yet the public demands sugar because of its sweetness. Also the public wants its sugar white. To believe otherwise involves wishful thinking and is unrealistic. Brown sugar cannot compete in the national market with white sugar, nor can sorghum or molasses. Some samples of molasses are rich in vitamins, others are not, and much brown sugar and molasses contain material that is undesirable.

Our country literally is a land flowing with milk and honey, but the milk, as I have said, is largely unconsumed, and the honey is in the form of refined sugar. Why not ask the sugar to carry the milk, and thereby provide sugar with the vitamins necessary to make its energy effective? Were each average daily per capita portion of sugar (five and one-half ounces) to be combined with only a little more than an ounce of skim milk solids, we should improve the American diet to the extent of including in it the equivalent of a pint of skim milk. For most cooking purposes the presence of 22 per cent of skim milk solids in sugar would be advantageous rather than otherwise. I can foresee objections from soda pop fanciers and those who like their liquors clear. The answer for them might be to use whey solids. Whey will go into a fairly clear solution. Whey represents the milk less casein. The lactalbumin, which contains all the biologically necessary amino-acids, remains, as does most of the content of minerals and water soluble vitamins. Whey is produced in enormous quantities as a by-product in the manufacture of cheese, and although some of it finds a market in poultry feed, it mostly today is not used for any purpose.

ASCORBIC ACID (VITAMIN C)

Were all flour to be "enriched" as now is recommended, were all edible fats to be fortified with vitamins A and D to reasonable limits, and if little more than an ounce of the solids of milk or whey could be incorporated in everybody's diet, thiamine, riboflavin, nicotinic acid, iron, calcium, vitamin A, vitamin D, and at least a minimal quota of all the biologically necessary amino-acids would be automatically provided.* Remaining for attention is ascorbic acid, the antiscorvy vitamin, vitamin C. If we can also arrange for its supply we shall have corrected, in all probability, the dietary deficiencies which mainly confront us. There may be other factors to think about later, but proof of their significance in human nutrition, or for their absence from even poor American diets, is not in the evidence today. In any case, as soon as the millers have learned how to mill a white flour which retains all the nutrients of wheat grain, we shall have no need to worry about other factors. They will be found in such flour.

Vitamin C, ascorbic acid, however, remains a problem. It is an old problem. Scurvy is said to have dogged the Crusaders. It is thought to have contributed more than anything else to the failure of the Vikings to colonize America. Directly, or indirectly, by predisposing to infections, scurvy has caused more loss of life in past wars than all the engines of war combined. It is said to have hastened the tragedy of the siege of Kut, to have weakened the British at Gallipoli in 1918, and to have contributed importantly to the collapse of Germany. Forewarned by this experience the Germans are said to have built up a huge reserve of synthetic ascorbic acid for this war.

Ascorbic acid is sensitive to oxidation. It cannot be heated without great loss and for this reason is little suited for fortification of any staple food. However, we have in our country vast supplies of citrus fruits and an abundance of tomatoes, all very acceptable to consumers. The problem is one of distribution. Subsidy may be necessary. Economies probably could be effected by suitable processing of the juices. Also, potatoes are a fair source of this important substance, and potatoes are abundant and inexpensive.

THE SCIENCE OF NUTRITION AN INSTRUMENT OF SOCIAL POLICY

A program such as that proposed would create the nutritional environment desired, in which to go wrong in nutrition would be difficult. The inexpensive staple foods which everybody eats would provide at least a minimal requirement of all the vitamins, minerals and amino-acids, and the balance then would easily be secured from whatever other foods were chosen to complete the diet.

* More iodine is needed in goiter regions, the states bordering on the Great Lakes and some mountain states. An adequate supply can be obtained by using iodized salt (one part sodium or potassium iodide to 5000 parts salt). Use of such salt has long been recommended by the Council on Foods and Nutrition of the American Medical Association.

The program, instead of provoking the opposition of the industries affected, should win their wholehearted coöperation, as it has in the case of the millers and bakers. Food habits, so difficult to change, should interfere scarcely at all. We still would have white flour, white bread, white sugar, margarine, and lard, but these would be good flour, good bread, good sugar and good fat. Malnutrition in such circumstances should vanish as a public problem, and with it undoubtedly would go much other disease.

The day has come when the science of nutrition must be recognized as an instrument of social policy. To put existing knowledge of nutrition to work is a duty, now, and with willingness on the part of government to coöperate with science and industry, enlightened procedure by industry and vigorous leadership by those who have influence on public opinion this will be done.

THE CONCENTRATION OF ARSENIC IN TISSUES AND THE EXCRETION OF ARSENIC BY EX- PERIMENTAL ANIMALS FOLLOWING INTRAVENOUS INJECTION OF MASSIVE DOSES OF MAPHARSEN *

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THE use of massive doses of arsenicals, given by the intravenous drip method, in the treatment of syphilis by Hyman, Chargin, Leifer and their co-workers¹ has stimulated renewed interest and effort directed toward improvement of the generally accepted plans for treatment of this disease. The advantages of reducing the time during which treatment must be continued consecutively and of rapidly stopping the possibility of spreading the disease are self evident. The need of information concerning the distribution of arsenic in the body following injection of large amounts within short periods is conspicuous. The relationship between concentrations of arsenic and its spirochetocidal effect, and its toxic effect upon various tissues should be determined.

The experiments, upon which this report is based, were undertaken for the purpose of repeating as nearly as possible in dogs the treatment used and described by the authors mentioned above. Arsenoxide ("mapharsen") was given in amounts comparable to those used in the treatment of patients by Hyman et al. The amount of arsenic excreted in the urine and feces, and the concentrations in the blood were determined during the experiment. Animals were sacrificed at various stages of the injections, concentration of arsenic in tissues determined and histological studies of numerous tissues made.

Adult male dogs weighing between 8 and 33 kilograms were used. The animals were fed a diet of canned dog food and given as much water as desired during the times when they were not actually receiving the injections of mapharsen.

During the intravenous injections it was necessary to have the dogs under nembutal anesthesia which at all times was as light as possible. All injections were made into the external jugular veins. For one half hour mapharsen dissolved in 5 per cent glucose was given, followed by 5 per cent glucose alone for one hour. This was repeated for a total of 10 times during the day. The rate of flow was such that the animal received 50 c.c. of fluid

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per hour. The dosage of mapharsen was 0.4 mg. per kilogram of body weight per hour and one half. A full course of treatment consisted of ten such doses daily for four days. Thus a dog at the end of four days would have received 16 mg. of mapharsen per kilogram of body weight, which is the equivalent of giving a man of 60 kilograms a total of 960 mg. of mapharsen.

Urine was collected through a retention catheter. All feces were saved for arsenic determinations. Blood and urine specimens for arsenic determinations were taken before each day's injection started and just before the fourth, seventh, and tenth mapharsen doses of each day. In some cases

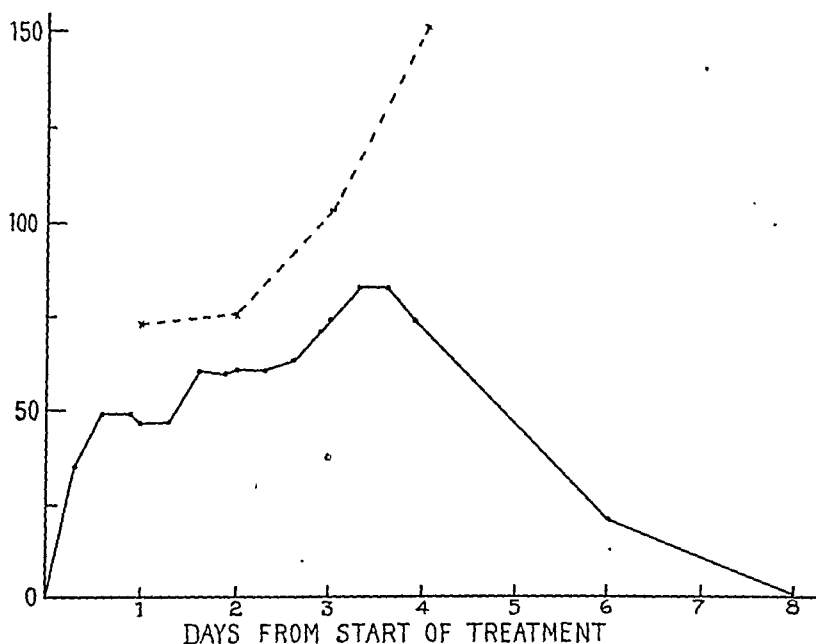


FIG. 1. Whole blood arsenic micrograms per 100 c.c. Solid line = one hour after mapharsen; broken line = one half hour after mapharsen.

specimens were taken one half hour after the finish of the last mapharsen of the day.

Animals were sacrificed at the end of one, two, three, and four days of treatment, and four, eight, and sixteen days following four days' treatment. When sacrificed at the end of a day's treatment, the animals were killed one hour after the start of the last mapharsen injection so that they received glucose alone for one half hour after the last injection of arsenic had been finished. Animals were sacrificed by increasing the anesthetic, and cutting the aorta just distal to the renal arteries so that as much blood as possible would be removed from the tissues.

Whenever possible duplicate specimens of tissue were taken for arsenic determinations, which were done by the method of Chaney and Magnuson.² Blocks for histological examination were fixed in Zenker's solution.

Eighteen animals were used in all, but complete analyses are available on but nine. Two animals died from overdosage of anesthetic at the end of five and of seven injections of arsenic. One dog, sacrificed on the third day of treatment, was found to have pneumonia. In view of the suggestion that fever be employed with this form of therapy, it is interesting to note that this dog had much higher concentrations of arsenic in nearly all his tissues than any other animal treated in this study. Three animals that received neoarsphenamine, one that received a small dosage of mapharsen, and two animals used in the first part of the experiment on whom technical difficulties in analysis were encountered, are not included. One animal was given glucose and anesthetic only and was used as a control.

The nine animals on which complete analyses are available are divided as follows: one each for the control, one, two, three and four days of treatment and for four and sixteen days following treatment and two for eight days following treatment.

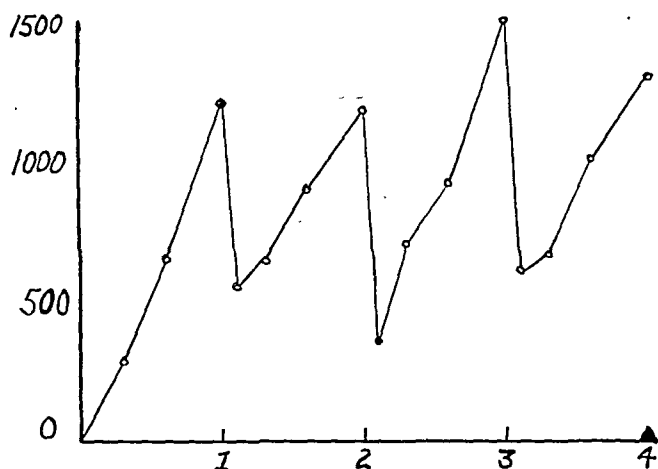


FIG. 2. Urinary excretion. Micrograms per 10 kg. body weight.

The amount of arsenic in micrograms per 100 c.c. found in whole blood is indicated in figure 1. The solid line represents samples taken just before the next dose of mapharsen was to be started. These values should represent the lowest level of arsenic during that particular time period. The values on the broken line represent samples taken at the end of the day one half hour after the finish of the last dose of mapharsen. It may be seen that these values are considerably higher than the minimum blood values. Attention should be called to the fact that during the eight hour night period when no arsenic was administered the blood arsenic failed to drop below the value obtained only an hour after the ninth dose of the previous day. Even two days after cessation of treatment the whole blood was found to contain approximately 20 micrograms of arsenic per 100 c.c.

The amount of arsenic excreted in the urine in micrograms per 10 kilograms of body weight is represented in figure 2. Unfortunately on some

occasions urine was lost during the night, and facilities were not available for the collection of urine following the four day injection period. It may be seen that the excretion increases during the day and that the total excretion increases from day to day. Expressed as percentage of the total amount of arsenic given to the end of that day the urinary excretion was as follows:

Per cent of arsenic given	Day			
	1	2	3	4
	18.8	24.5	27.3	27.9

There appears to be a slight lag in the excretion, though this may be more apparent than real as the night urine is included with that of the following day.

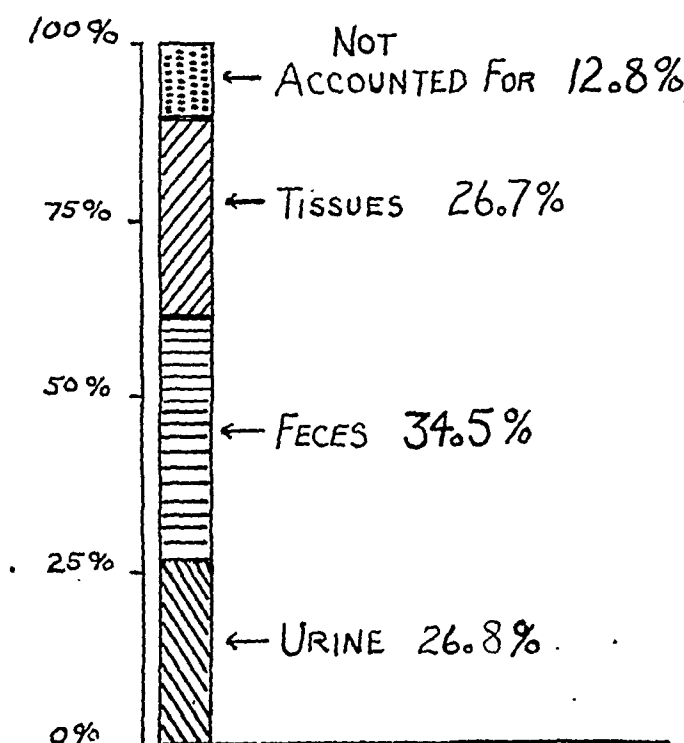


FIG. 3. Fate of arsenic in four day dog.

The amount of arsenic excreted and the distribution of that retained in the body of an animal that had received injection during each of four successive days, is indicated in figure 3. The amounts in the tissues are based upon the actual weights of the parenchymatous organs, with the weight of the muscles and bones estimated at 50 per cent and 25 per cent, respectively, of the total body weight. The amount unaccounted for probably represents tissues

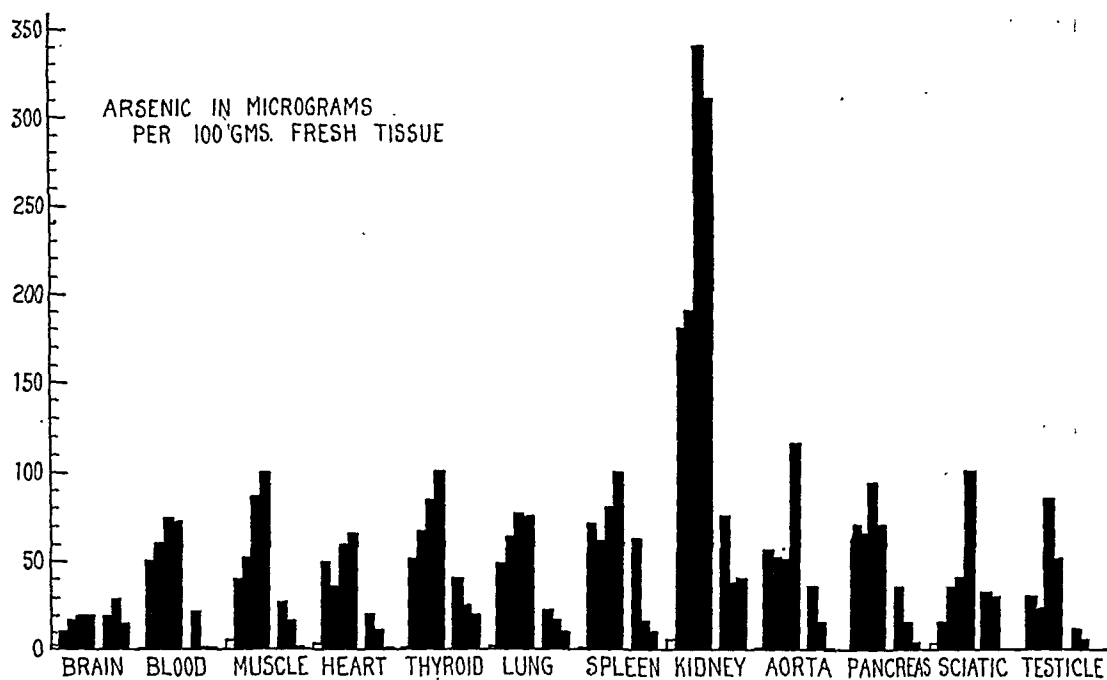


FIG. 4.

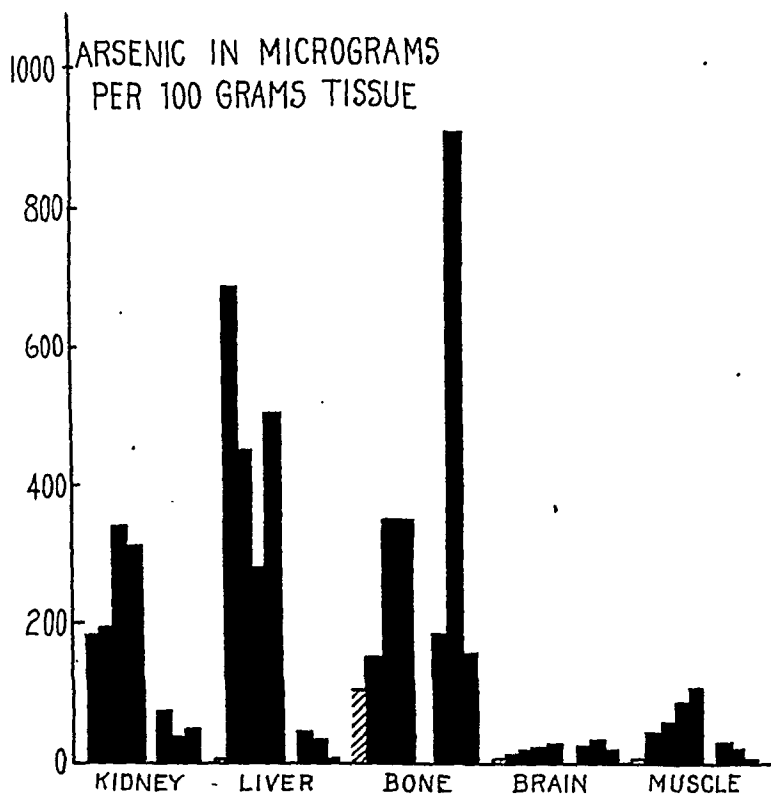


FIG. 5.

not analyzed, e.g. skin, bowel wall, plus some losses which occurred in the collection of urine and feces.

The amounts of arsenic found in the various tissues expressed as micrograms of arsenic per 100 grams of fresh tissue are indicated in figures 4 and 5. The first block represents the amount found in the control, and the next four the values found on each of the four successive days of treatment. Following this there is a break to indicate cessation of treatment, and each of the following blocks represents amounts found four, eight, and sixteen days following the cessation of treatment. The blood level is that obtained just before the tenth dose of mapharsen of that particular day, and is the same as that represented by the solid line in figure 1. It is inserted here for comparison. These values are presented in tabular form in table 1, which also contains the results obtained by analysis of bile aspirated from the gall-bladder.

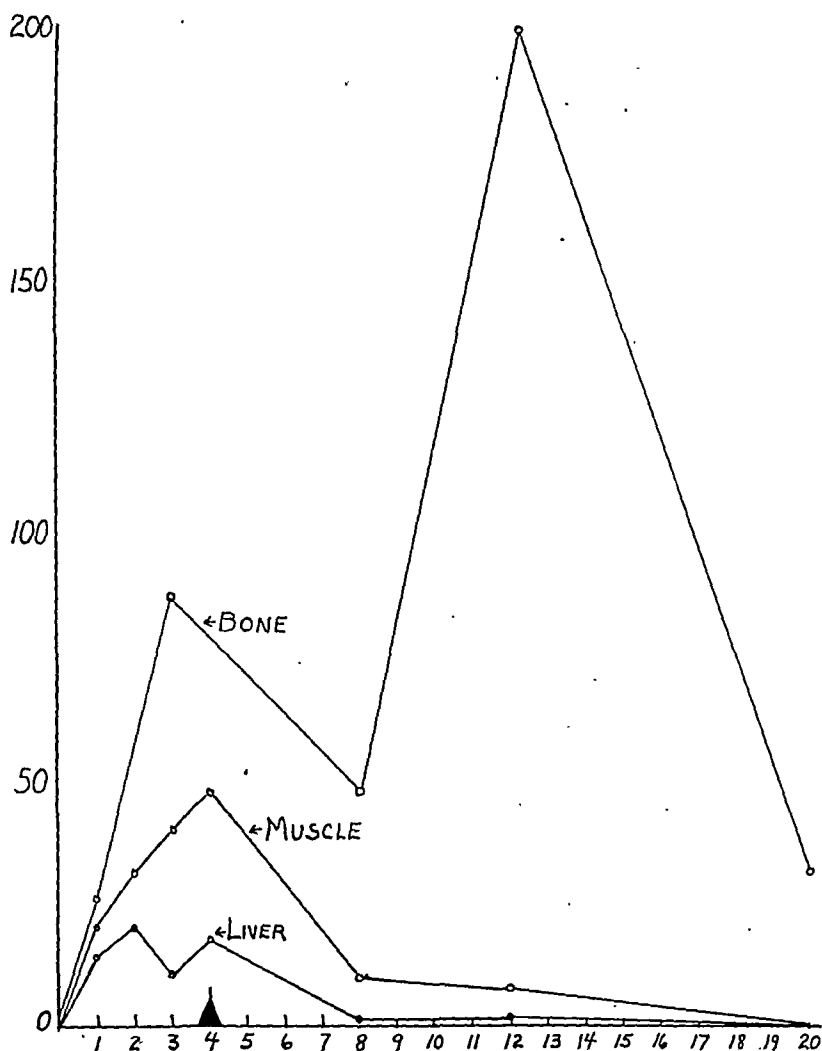


FIG. 6. Arsenic in micrograms per 100 grams multiplied by organ or tissue weight \div total body weight.

The results of an attempt to estimate the total amounts of arsenic in the various organs and tissues are presented in figure 6. This was done to emphasize the magnitude of the storage of arsenic in the skeletal and muscular systems, a fact which is not readily appreciated when the results are expressed in micrograms per cent of tissue.

The microscopic sections from tissues of these animals were examined by Dr. E. M. Hall of the Department of Pathology, who reported that sections of the brain, heart, spleen, and lung failed to show any significant changes. The liver cells tended to be swollen and pale probably due to high glycogen content. The nuclei of the hepatic cells were well preserved. In the kidneys the only findings were a diffuse granular swelling of the tubular epithelium with moderate karyolysis. The findings in the livers and kidneys were interpreted as being minimal and entirely reversible.

TABLE I

Arsenic in Tissues, Expressed as Micrograms of Arsenic per 100 Gm. Fresh Tissue

Tissue	Days of Treatment							
	Control	1 day	2 days	3 days	4 days	4 days after R	8 days after R	16 days after R
Heart	4	49	35	58	64	20	12	0
Lung	0	48	63	76	75	22	15	10
Liver	6	684	445	263	535	46	36	8
Gall-bladder bile (total in bile)	2	—	—	5025	1600	6	11	3
Spleen	0	72	60	80	100	63	17	10
Kidney	5	182	190	340	310	75	37	41
Pancreas	0	70	65	93	70	24	12	4
Aorta	0	56	51	50	116	34	15	0
Skeletal ms.	5	38	51	85	95	26	16	0
Testicle	0	31	22	85	53	12	6	6
Peripheral nerve	4	15	35	39	101	31	30	—
Thyroid	0	51	67	84	101	41	27	21
Bone (femur)	0-100	148	—	350	—	158	761	170
Brain	3	10	16	18	18	18	28	14

DISCUSSION

The amounts of arsenic found in the blood indicate that following repeated doses of mapharsen the arsenic does not leave the blood as rapidly as it does following single doses of neoarsphenamine³ and that by frequently repeated doses a high concentration of arsenic may be maintained. Such a result is in keeping with the findings of Underhill and Horn,⁴ who found a "lag" in the elimination of neoarsphenamine from the blood when repeated injections were given at four day intervals. This accumulation, as observed in our experiments apparently is not due to kidney damage, as indicated by the continued excretion of large amounts of arsenic in the urine and the absence of histological evidence of important changes in these organs. It may be assumed that the tissues reach a saturation point after which they absorb less arsenic from the blood stream.

The maximum concentrations of arsenic in the blood during and immediately following these injections were not determined, as we were interested primarily in the minimum levels maintained. That the maxima became progressively higher is suggested by the values obtained one half hour after the tenth dose of each day. By the end of the fourth day this level had reached 150 micrograms per cent of arsenic in contrast to a level of 73 micrograms per cent at the end of the first day.

During the treatment period there was a slightly higher excretion of arsenic through the urine and feces in these animals given mapharsen than in the patients given neoarsphenamine by Hyman et al.¹ As with their patients, we found more arsenic excreted in the feces than in the urine. The so-called "normal" arsenic in feces and urine was so small in proportion to the amounts of arsenic with which we were dealing that for practical purposes it could be ignored. Feces and urine obtained before mapharsen was administered contained only traces of arsenic.

In view of the enormous concentrations of arsenic in the gall-bladder bile we believe that the greater part if not all of the arsenic contained in the feces reaches the bowel through the bile. Kuroda⁵ on the basis of a single biliary fistula experiment states that following intravenous neoarsphenamine 9/10 of the arsenic found in the feces is excreted in the bile. Bulmer⁶ had somewhat similar results with phenarsenamine. That the removal of arsenic by the liver and excretion in the bile must be quite efficient is indicated by the fact that the concentration of arsenic in the liver does not rise above the level reached during the first day of injection in spite of continued injection of large amounts during the next three days.

The concentrations of arsenic obtained in the tissues are most interesting. With but four exceptions, there is a tendency for the arsenic concentration in the tissues to parallel that of the blood. These four exceptions are brain, liver, kidney, and bone.

As has been found in other experiments with organic arsenicals, the penetration of arsenic into the brain is slight.^{12, 3, 13} That there was a slight penetration is clear, but equally striking is the fact that arsenic is removed from the brain much more slowly than from any other tissue.

The concentrations of arsenic in the liver and in the kidney are not surprising in view of the known excretory functions of these organs. That the concentration in the liver reaches a maximum during the first day must indicate that the capacity of the liver to excrete the arsenic through the bile is equal to, or greater than its capacity to selectively remove the arsenic from the blood stream.

Arsenic in the gall-bladder disappeared very rapidly following the cessation of mapharsen. The arsenic content of the liver dropped much more rapidly than that of the kidney. This apparently indicates that after the initial large amounts of arsenic have been excreted, the major portion of the remaining arsenic is excreted through the kidney rather than the liver.

The deposition of arsenic in the bones is a phenomenon which has been emphasized but little, especially in the American literature. Bulmer⁶ found a considerable deposition of arsenic in the bones following the injection of phenarsenamine. Fuchs⁷ and Popp⁸ reported accumulation of arsenic in the long bones following inorganic arsenic administration to human beings. Boos and Werby⁹ state, "Our study seemed to show that when the individual lived only a few hours (after poisoning) the amount in bone was quite small, whereas the bones of those cases who had lived several days showed a substantial quantity of arsenic." These authors also found the arsenic content of the bones of food animals (beef, pork) to be as high as 8.0 parts of As_2O_3 per million.

These findings are in accord with our observations that there is an accumulation of arsenic in bones which reaches its maximum after arsenic administration has been stopped and while the arsenic concentration in other tissues is falling. This would indicate a secondary mobilization of the arsenic with secondary deposition in the bone.

Some determinations were made on the bone marrow but are too few in number to be conclusive. There is apparently a considerable accumulation of arsenic in the marrow, but to a smaller degree than in the bone itself.

The cross hatched block in the bone analyses shown in figure 6 represents the maximum blank obtained from numerous bones of dogs and human autopsy material. These were analyzed not only by our method but by the A. O. A. C. official Gutzeit method as well. The determination of arsenic in bones offers considerable technical difficulties. The high content of pyridine compounds interferes with the evolution of arsine in the various modifications of the Gutzeit and Marsh tests.¹¹ With our method special care must be taken to avoid contamination by phosphorus. This can be readily accomplished by a double distillation procedure.

One is of course tempted to estimate whether the concentrations of arsenic obtained in the tissues are spirocheticidal. Eagle¹⁰ has determined that mapharsen, "arsenoxide," in the presence of the edematous ooze from a rabbit chancre has a definite antispirechetal action within 1 to 2 hours at room temperature (25 to 34° C.) in concentrations of approximately 1:1,000,000 to 1:4,000,000. Taking 1:1,000,000 as the spirocheticidal level would mean a level of 29 micrograms of arsenic per 100 grams of fresh tissue calculating mapharsen on the basis of 29 per cent arsenic content and further assuming that all of the arsenic in the tissues is in the form of mapharsen. This would mean that all of the tissues examined with the exception of the central nervous system had during the four day treatment period concentrations of arsenic which were spirocheticidal. However, we have no way of proving that the arsenic present was in the form of "arsenoxide" or some other antispirechetal form so that the above assumptions are not entirely valid. On the other hand such assumptions may not be totally invalid, for in Eagle's experiments the concentration of "arsenoxide"

as such was known only at the beginning of the experiments and how rapidly the "arsenoxide" may have broken down into therapeutically inert forms is not known.

Of definite significance is the absence of serious damage to the tissues by the large doses of mapharsen as seen in the microscopic sections. While these findings are very encouraging, it is emphasized once again that this is but a single step of the many suggested at the beginning of this paper which should be taken before more general use is made of this method in the treatment of human syphilis.

SUMMARY AND CONCLUSIONS

1. By the continuous intravenous drip method dogs were given doses of mapharsen comparable to those proposed for the treatment of syphilis in man.
2. The concentrations of arsenic obtained in the blood, urine, and various tissues are presented and their significance is discussed.
3. Histological examination of the tissues revealed but minimal changes.

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The assistance of Dr. E. M. Hall who examined the microscopic sections from tissues of these animals is gratefully acknowledged.

The mapharsen used in these experiments was supplied by Parke, Davis and Company.

BIBLIOGRAPHY

1. HYMAN, H. T., CHARGIN, L., and LEIFER, W.: Massive dose arsenotherapy of syphilis by the intravenous drip method, *Am. Jr. Syph., Gon. and Ven. Dis.*, 1939, xxiii, 685-691.
- HYMAN, H. T., CHARGIN, L., RICE, J. L., and LEIFER, W.: Massive dose chemotherapy of early syphilis by the intravenous drip method, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1208-1214.
- TZANCK, A., DUPERRAT, and LEWI, S.: *Intensive treatment with neoarsphenamine given intravenously at a very slow rate*, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1938, liv, 268.
2. CHANEY, A. L., and MAGNUSON, H. J.: The colorimetric microdetermination of arsenic, *Jr. Ind. and Eng. Chem., Anal. Ed.*, 1940, xii, 691-693.
3. KOLLS, A. C., and YOUNG, J. B.: Quantitative studies with arsphenamine. II. Distribution and excretion after intravenous injection, *Bull. Johns Hopkins Hosp.*, 1923, xxxiv, 181-184.
4. UNDERHILL, F. P., and HORN, M.: Concentration of arsenic in blood subsequent to serial administration of neoarsphenamine, *Proc. Soc. Exper. Biol. and Med.*, 1927, xxv, 138-139.
5. KURODA, T.: Über die Ausscheidung des Arsens durch die Galle, *Arch. f. exper. Path. u. Pharmacol.*, 1927, cxx, 330-340.
6. BULMER, F. M. R.: Experimental research on distribution and elimination of organic arsenic compounds after intravenous administration, *Jr. Pharmacol. and Exper. Therap.*, 1923, xxi, 301-311.
7. FUCHS, LEOPOLD: Beitrag zur Verteilung des Arsens im Organismus nach percutaner Resorption therapeutischer Dosen, *Deutsch. Ztschr. f. d. ges. gerichtl. Med.*, 1932, xix, 280-284.

8. POPP, HANS: Distribution of arsenic in the bones of the human body, *Z. Angew. Chem.*, 1931, xliv, 658-659.
9. BOOS, WM. F., and WERBY, A. B.: Arsenic in human tissues and food animals. I. So-called normal arsenic, *New Eng. Jr. Med.*, 1935, ccxiii, 520-524.
10. EAGLE, H.: Minimal effective concentrations of arsenic and bismuth compounds on *Treponema pallidum* in vitro in relation to therapeutic dose, *Am. Jr. Syph., Gon. and Ven. Dis.*, 1939, xxiii, 310-318.
11. GROSS, C. R.: Interference of pyridine derivatives in arsenic determination, *Jr. Ind. and Eng. Chem., Anal. Ed.*, 1933, v, 58-60.
12. RUDOLF, R. D., and BULMER, F. M. R.: Fate of arsenic after intravenous or intrathecal injection, *Am. Jr. Med. Sci.*, 1923, clxv, 47-53.
13. UNDERHILL, F. P., and DIMICK, ALICE: The distribution of arsenic in the tissues after serial administration of neoarsphenamine, *Am. Jr. Physiol.*, 1928, lxxxiv, 56-60.

THE IMMEDIATE PROGNOSIS OF CONGESTIVE HEART FAILURE *

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IN a previous study¹ the underlying causes and precipitating factors in 1000 patients with congestive heart failure were analyzed, and in 748 patients followed for three months or longer the immediate prognosis was appraised. Patients who died or who remained in failure at rest during the minimal three months' follow-up period were considered together as a single group and designated as having a poor outcome. The results of this study indicated that the immediate prognosis was, in general, independent of the underlying type of heart disease. The precipitating cause of failure, however, played an important rôle in prognosticating the outcome, not only because some of the precipitating causes were uncontrollable, but also because the apparent benignity or malignancy of any precipitating factor is a fair measure of the myocardial reserve before the actual onset of congestion. Thus when failure is precipitated by a relatively mild respiratory infection, it seems obvious that the myocardial reserve must have been already very low. On the other hand, auricular fibrillation with a very rapid ventricular rate can precipitate failure in a diseased heart with high reserve and probably even occasionally in a heart which is otherwise apparently normal. Consequently, with adequate control of the heart rate, a good deal of myocardial reserve may be regained, although naturally tachycardia of any sort may also excite failure when the reserve is low.

Figures 1 and 2, arranged according to underlying causes and exciting factors respectively, will serve to illustrate graphically the proportion of poor results in the 748 patients adequately followed.

That the prognosis of congestive failure may be modified by the presence of complications was alluded to in the previous paper,¹ where it was pointed out that such complications will necessarily cloud the exact evaluation of the prognosis of heart failure alone. There were 242 patients with significant complicating pathological conditions, and in 71 instances the complication was totally unrelated to the heart failure or to the cardiovascular system. The complications were, of course, of varying importance and in a few instances the heart failure might better, perhaps, have been classified as a complication of some other disease of more immediate importance. Of this group with complications, 84 per cent did poorly, as compared to 63 per cent for the entire series.

The more frequently encountered complications include embolism (peripheral or pulmonary), anemia, diabetes, cerebral vascular accidents,

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THE IMMEDIATE PRECIPITATING CAUSE

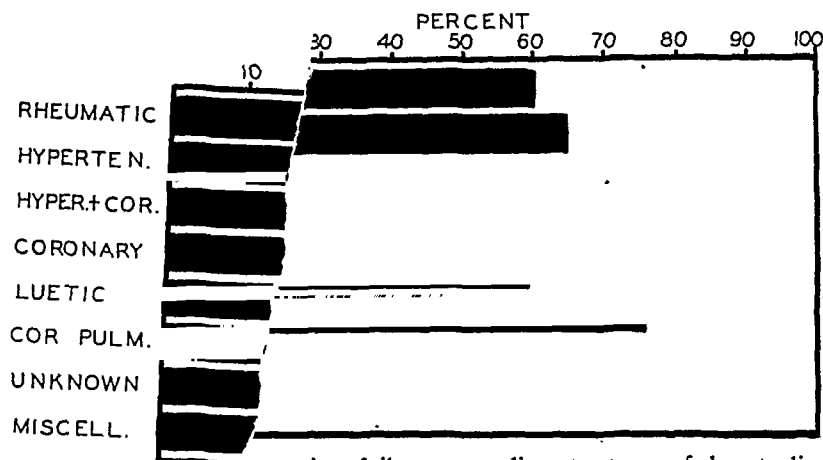


FIG. 1. Poor outcome in congestive failure according to type of heart disease, i.e., patients who died or remained in failure at rest during a minimum three months' follow-up period. Miscellaneous causes include congenital heart disease, calcareous aortic stenosis, tension which could not be classified as with or without complicating coronary diseases

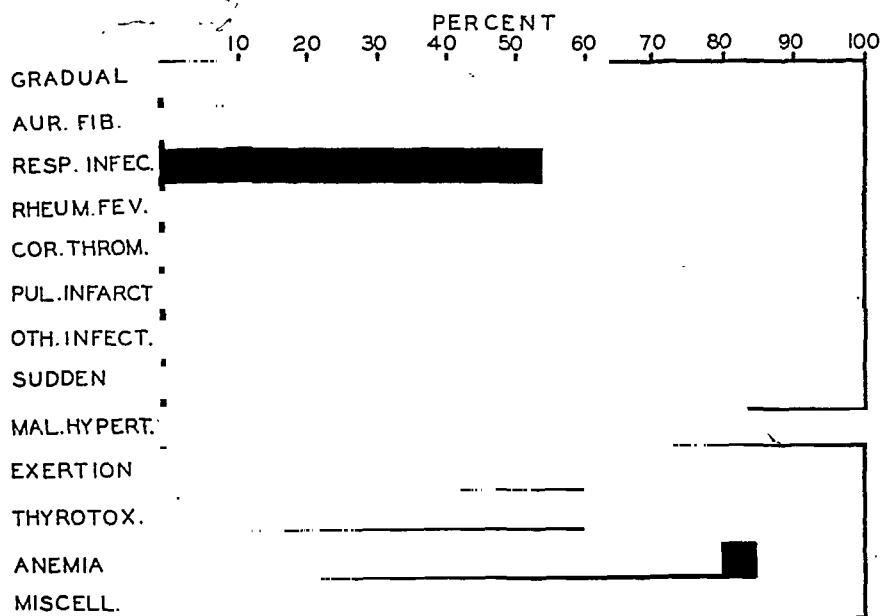


FIG. 2. Poor outcome in congestive failure according to precipitating cause of failure, i.e., patients who died or remained in failure at rest during a minimum three months' follow-up period. Miscellaneous causes include surgical operation, paroxysmal tachycardia, pulmonary malignancy, pregnancy, bronchial asthma, emotion, trauma, "indigestion" or gall-bladder colic, and administration of an excess amount of fluid.

and pneumonia. Pulmonary embolism with infarction was by far the commonest complication, having been recognized as a complication in 60 cases of the entire series of 1000 patients with congestive heart failure, in addition to 33 instances in which it was considered to be the precipitating cause of failure. All of the underlying types of heart disease appear to be liable to pulmonary infarction, although in patients with rheumatic heart disease the

complication makes up a larger part of the total number of complications than in those with other types of underlying heart disease.

The purpose of the present communication is to emphasize additional factors of importance in determining the immediate prognosis in the same group of 748 patients with congestive heart failure. We are including also data on an additional group of 167 patients with acute coronary occlusion, in whom congestive failure was associated in 111.

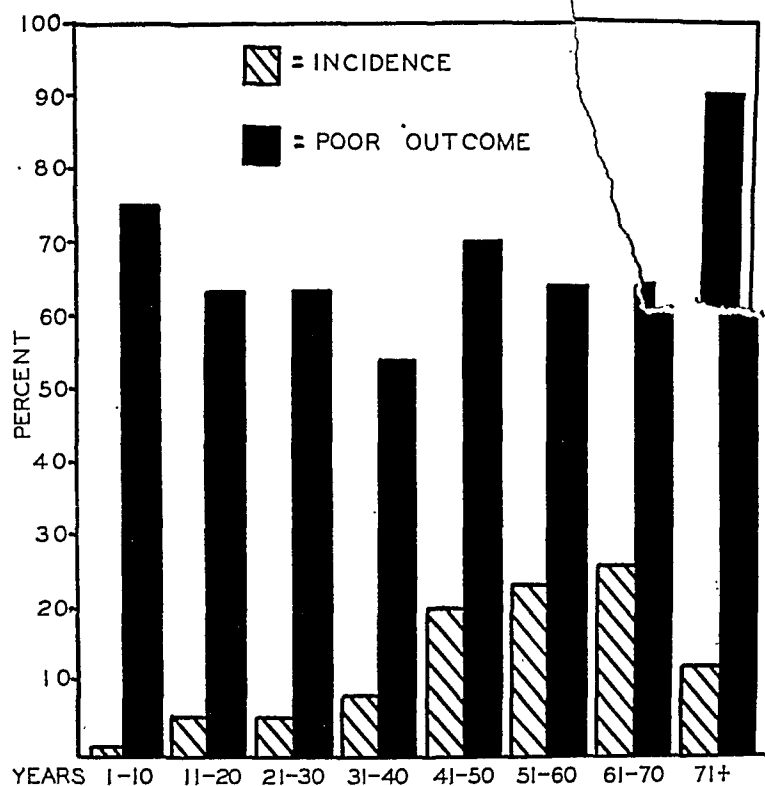


FIG. 3. Age incidence and percentage of poor outcome of congestive failure.

AGE INCIDENCE

Figure 3 has been constructed to show the distribution of cases by decades and the relation which age bears to recovery. The peak of the incidence of congestive heart failure lies between the ages of 40 and 70. The outcome was fairly constant for all age groups and corresponds closely to the outcome for all types of heart disease, with the exception of three peaks. Seventy-five per cent of a small group of children up to 10 years old did poorly. All but one of these had severe rheumatic infection with failure, and such an outcome might be expected. The peak during the fifth decade is not so easily explained. Since there is no great difference in the outcome for the various underlying factors, and since this age group fairly well represents them all, it is apparent that a preponderance of any one type of heart

disease will not explain this observation. When, however, the exciting factors were listed according to age distribution and outcome, a possible explanation of the difference between the age group from 41-50 and the adjacent groups that apparently do better appeared. Of those patients whose failure began gradually, as it did in 30 per cent of the patients in the fifth decade, 85 per cent did poorly, as compared to 64 per cent for all ages combined. The explanation which occurs to one at once is that these are the people who are in the prime of life and are busily engaged as breadwinners and homemakers and that, as such, they neglect themselves until failure is well advanced. Whether this or another more occult reason is the true one must remain unanswered at present. The difference, in any event, is slight and may be largely fortuitous. The somewhat lower percentage of poor results in the preceding decade (31-40) is doubtless in part, at least, attributable to the greater incidence of auricular fibrillation (exclusive of cases associated with acute rheumatic fever) as a precipitating cause (15 per cent in decade 31-40, 8 per cent in decade 21-30, and 7 per cent in decade 41-50), since figure 2 shows that auricular fibrillation carries the best prognosis of all exciting factors.

The third peak occurs in the group of patients over 70 years of age. This increase in the percentage of patients with poor outcome is true for all cases in this age group, regardless of the precipitating factor. For example, 82 per cent in this group do poorly when failure occurs gradually as compared with 64 per cent for all ages combined. Coronary thrombosis with myocardial failure was 100 per cent fatal in this group, while in all age groups combined 78 per cent did poorly. Auricular fibrillation, which for all ages has 49 per cent poor recovery, shows 100 per cent poor results in patients over 70. Respiratory infection, with a recovery rate of almost 50 per cent for all groups, results in failure from which compensation is not regained in 75 per cent of the elderly patients. Thus it is apparent, and not very surprising, that regardless of other circumstances, congestive heart failure in patients over 70 years of age carries a grave prognosis.

Figures 4 and 5 were constructed to show the average age incidence for the more common underlying causes and precipitating factors. There is, of course, considerable scatter, but the charts represent the general trends and serve to illustrate some points of interest. Rheumatic and coronary disease represent the two extreme age groups of the underlying causes of failure (figure 4). Further, it appears that failure occurs in uncomplicated hypertension at a significantly earlier age than it does in hypertension complicated by coronary disease. The age incidence in the latter group is close to that of coronary disease alone, and, *a priori*, heart failure would seem to be more dependent on the coronary disease than on the hypertension.

Rheumatic fever and malignant hypertension, as is well known, more commonly afflict young people (figure 5). Auricular fibrillation, too, precipitates failure in relatively youthful patients, and this may, in part, account

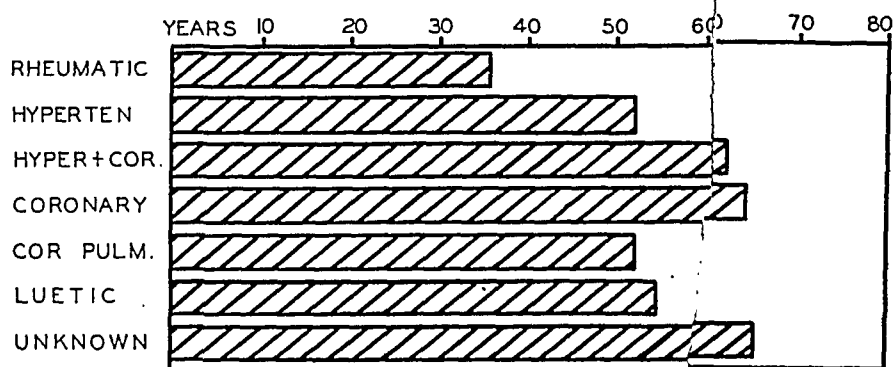


FIG. 4. Average age incidence of each of the underlying causes of congestive heart failure, at the time of onset of the failure.

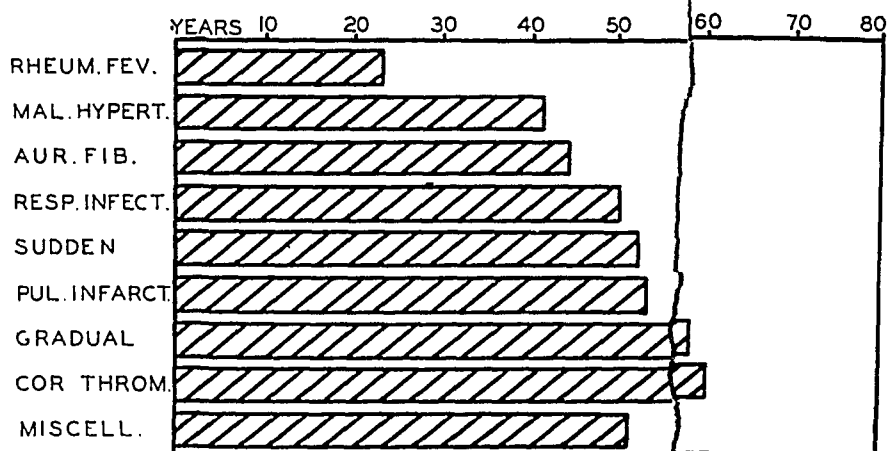


FIG. 5. Average age incidence of some of the more important precipitating factors, at the time of onset of the failure.

for the relatively good prognosis of auricular fibrillation. The average age incidence for failure precipitated by coronary thrombosis was the highest of all known exciting causes.

CORONARY THROMBOSIS AND HEART FAILURE

In the previous study of congestive failure¹ it was observed that when coronary thrombosis precipitated congestive failure there appeared to be no difference in the outcome, whether the patient was also hypertensive or not. There were 63 patients with coronary disease and congestive failure who had hypertension and 63 who had normal, or low, blood pressure, and in each group the outcome was poor in about 75 percent of the cases. It seemed unlikely, at first, that patients with the additional handicap of hypertension would fare as well as those without. The obvious source of error, it was thought, might lie in the group of patients with unknown preëxisting hypertension, but with normal or low blood pressure on admission to the

hospital. Accordingly, this factor was investigated in 167 patients* with coronary occlusion, in whom the previous blood pressure was known. Seventy-seven patients were known to have had hypertension, and 90 known to have had normal blood pressure previous to the coronary occlusion. It is apparent from figure 6 that when patients with hypertension reach the

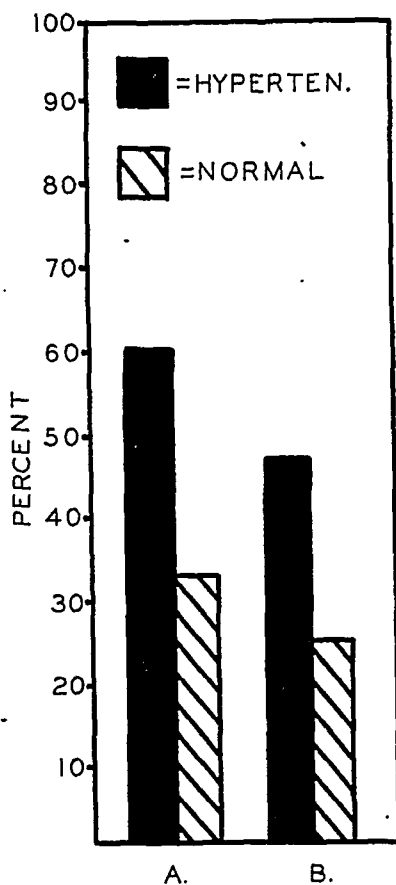


FIG. 6. Coronary occlusion and congestive heart failure. Percentage of patients with signs or symptoms of congestive failure before the onset of clinical coronary occlusion is labelled A; percentage of patients in whom congestive failure was precipitated by coronary occlusion is labelled B. It is evident that patients with hypertension not only are closer to congestive failure before coronary occlusion but also are more frequently precipitated into failure by occlusion than are patients with coronary disease alone.

age at which coronary occlusion is likely to occur, they already are on the edge of failure, for 60 per cent of the patients in this group had signs or symptoms of decreased myocardial reserve before the coronary occlusion, as compared to 33 per cent of non-hypertensive patients with coronary disease who exhibited similar loss of myocardial reserve antedating the occlusion. Furthermore, of the patients who had no evident antecedent failure, a considerably greater number of the hypertensives than of the non-hypertensives

* We are indebted to Dr. E. F. Bland for making the data on 125 of these patients available to us.

were precipitated into failure by the occlusion. Since there is general agreement that when congestive failure accompanies coronary thrombosis the outlook is grave, it seems to follow that patients with hypertension and coronary occlusion will do less well than those with normal blood pressure. Certainly there seems to be little support in this series of cases for Levine's⁷ opinion that hypertensive patients with coronary occlusion tend to fare better than do those with a normal blood pressure. To be sure, there are factors other than congestive failure which determine the prognosis of coronary thrombosis, but congestive failure would seem to be one of the most important prognostic leads in comparing hypertensive with non-hypertensive subjects.

In the latter series of patients with coronary occlusion and congestive failure, as well as in the original study, the proportion of cases that did poorly was equal in the hypertensive and non-hypertensive groups. Seventy-five per cent of patients who exhibit congestive failure accompanying coronary occlusion may be expected to die or to remain seriously crippled by congestive failure, whether antecedent hypertension was present or not. It seems, therefore, that once failure has developed in patients with coronary disease alone or in those with hypertension in addition to coronary disease, the myocardium has an equal capacity for regaining its reserve in both instances. Recovery may be hampered in the one, because of long-continued strain with cardiac hypertrophy and relative coronary insufficiency; in the other, because of generalized narrowing of all the coronary vessels with perhaps several actually occluded. Figure 1 indicates that this is true for all cases of coronary disease, irrespective of the precipitating cause of failure. It is of further interest that the proportion of patients with hypertension alone who do poorly is equal to that of patients with coronary disease alone, or of those with combined hypertension and coronary disease, despite the fact that the average age at the onset of failure in patients with hypertension alone is ten years earlier than in those with coronary disease in addition to hypertension (figure 4).

Since the conclusion that the prognosis of patients with hypertension and coronary occlusion is poorer than of non-hypertensive cases with occlusion differs from opinions previously expressed, and since it was suspected that a fall in blood pressure from hypertensive to normal levels may have been a source of error in previous studies, our patients were divided into those with and those without a significant fall in blood pressure. Of the 77 known hypertensives, there was a significant fall of blood pressure with coronary occlusion in 83 per cent, *and in 75 per cent of these it fell to normal or below.* In the group of patients known to be non-hypertensive, a substantial fall in pressure occurred in 50 per cent.

Figure 7 has been constructed to illustrate the frequency with which congestive failure eventuates when coronary occlusion is accompanied by a notable fall in blood pressure. It appears that when a material fall in pressure occurs, either because it reflects the severity of the attack or be-

cause in itself it may be partly due to failure of the myocardium, congestive failure more often ensues than when coronary occlusion is not attended by such a fall in blood pressure. The corollary necessarily follows that when a hypertensive patient remains hypertensive despite acute coronary occlusion, he will be less likely to develop congestive failure and, other things being

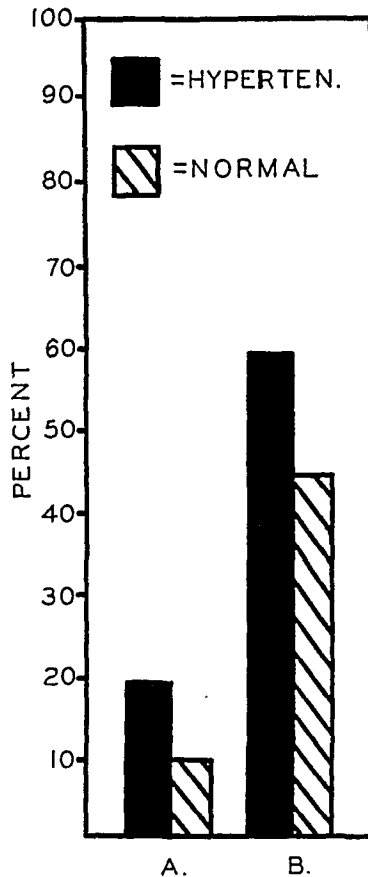


FIG. 7. Incidence of congestive failure precipitated by clinical coronary occlusion when the latter is not accompanied by a significant fall in blood pressure A, and when it is accompanied by a fall in blood pressure B. It appears that if the blood pressure remains elevated following coronary occlusion, congestive failure is less likely to follow.

equal, his prognosis will be better. It seems justifiable to conclude that failure to recognize the fact that coronary occlusion in patients with hypertension is less well borne than in non-hypertensives arises from the circumstance that the hypertensive subject is more likely to have a fall in pressure which, in the majority of cases, will be found to be normal following occlusion. The error of classifying such patients as non-hypertensives not only improves the statistics of the hypertensive group but in addition unfavorably weights the non-hypertensive group.

CARDIAC ENLARGEMENT AND PROGNOSIS

Attention to cardiac enlargement in heart failure has been centered largely on heart weight at postmortem examination, and, in general, a direct correlation between increasing weight and heart failure has been found. Thus Nathanson² found signs of failure in only 6.6 per cent of hearts weighing less than 400 grams, while failure was present in 63.2 per cent of those over 400 grams. Clawson and Bell³ found only three cases with a heart weight of less than 500 grams among 28 patients with congestive failure due to luetic aortic regurgitation, and these three had hearts weighing between 450 and 500 grams. The same authors⁴ found in 94 cases of failure due to hypertension that only 10 had heart weights below 450 grams and 23 had heart weights below 500 grams. Gross and Spark⁵ studied the relationship

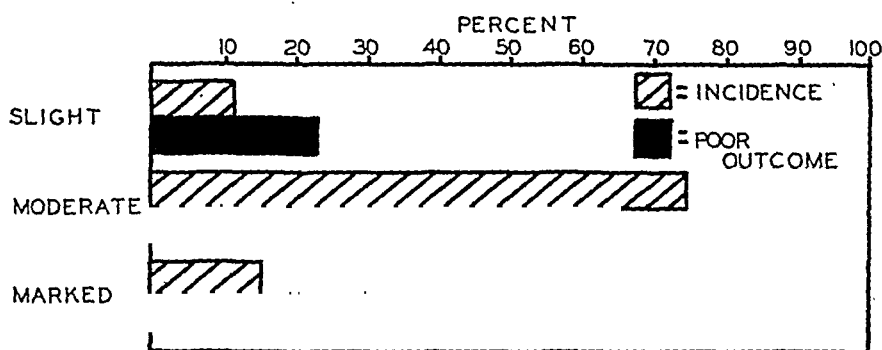


FIG. 8. Incidence of clinical cardiac enlargement and the relationship which it bears to outcome.

of hypertrophy to failure and concluded that the common denominator of all cases of heart failure, except that associated with acute inflammatory change, was a disproportion between the coronary blood flow and the bulk of cardiac muscle, and that increasing cardiac hypertrophy eventually outstrips its blood supply, thus resulting in myocardial failure. This concept has recently been challenged by Davis and Blumgart⁶ who believe that cardiac hypertrophy results from chronic congestive failure and that this accounts for the heavy hearts found post mortem in patients with failure. Gross and Spark were unable to correlate heart weight with the duration or severity of heart failure.

At the time the present case histories were studied, heart size was not particularly investigated, but in 277 cases the tabulated data contained information from which the heart size, as determined by physical examination and/or teleoroentgenogram, could subsequently be classified. The degree of enlargement was graded as slight when the apex of the heart was up to 1 cm. outside the midclavicular line, moderate when up to 3 cm., and marked when over 3 cm. outside the midclavicular line. This study appeared to be of especial interest because, first, the measurements were made during life and hence could be used prognostically, and, second, clinical enlargement is pre-

dominantly a measure of dilatation rather than of hypertrophy, a factor not hitherto adequately evaluated. Of the 277 cases, 187 were followed sufficiently long to provide an estimate of the immediate prognosis. The data are illustrated in figure 8 where it is clear that most patients fell into the group with moderate cardiac enlargement. There were a few patients with very large hearts and a few with only slight enlargement. It is also apparent in the figure that the latter group, on the whole, did very well, whereas the outcome became progressively poorer as the degree of enlargement increased. It is worthy of note, however, that even in the group with marked enlargement, 29 per cent made a fair or good immediate recovery.

SUMMARY AND CONCLUSIONS

The immediate prognosis in 748 patients with congestive heart failure has been studied and found, in general, to depend very little on the underlying type of heart disease, but, in varying degree, on the precipitating cause of failure, the patient's age, the degree of clinical cardiac enlargement, and the presence or absence of complications.

An additional analysis of the case histories of 77 known hypertensives and 90 known non-hypertensives with coronary thrombosis revealed that a greater percentage of hypertensive patients will develop congestive heart failure than will the non-hypertensives, and consequently the prognosis is poorer for the former group of patients when coronary occlusion occurs. Once failure develops, however, the outcome is the same for those with or without antecedent hypertension.

BIBLIOGRAPHY

1. BOYER, N. H., LEACH, C. E., and WHITE, P. D.: Underlying causes and precipitating factors of congestive heart failure. Symposium on the blood, heart and circulation, Am. Assoc. Adv. Sci., Publication No. 13, The Science Press, 1940, p. 203.
2. NATHANSON, M. H.: Disease of the coronary arteries, *Am. Jr. Med. Sci.*, 1925, clxx, 240.
3. CLAWSON, B. J., and BELL, E. T.: The heart in syphilitic aortitis, *Arch. Path.*, 1927, iv, 922.
4. BELL, E. T., and CLAWSON, B. J.: Primary (essential) hypertension, *Arch. Path.*, 1929, v, 939.
5. GROSS, H., and SPARK, C.: Coronary and extra-coronary factors in hypertensive heart failure, *Am. Heart Jr.*, 1937, xiv, 160.
6. DAVIS, D., and BLUMGART, H. L.: Cardiac hypertrophy—its relation to coronary arteriosclerosis and congestive heart failure, *ANN. INT. MED.*, 1937, xi, 1024.
7. LEVINE, S. A.: Coronary thrombosis—its various clinical features, 1931, Williams and Wilkins Co., Baltimore.

THE FREQUENCY AND CHARACTER OF URINARY TRACT INFECTIONS IN AN UNSELECTED GROUP OF WOMEN *

By CHARLES D. MARPLE, M.D., *San Rafael, California*

THIS study was prompted by the observation that positive urine cultures were obtained as a purely incidental finding from many of the women hospitalized on the Stanford Medical Service. It was the impression of the staff that many of these patients presented no symptoms referable to their urinary tracts. The questions which immediately arose were: What is the significance of these positive urine cultures and what is the frequency of urinary tract infections in this type of woman?

Interest in the incidence of and in the significance of urinary tract infections is far from being purely academic. Several investigators have pointed out a series of events, starting with the protean urinary tract infection and leading through pyelonephritis to renal damage and hypertension.¹

A fairly comprehensive, although by no means exhaustive, review of the literature on urinary tract infections failed to reveal any adequate studies on the incidence of these infections in the general population of a women's medical ward. Leischman² reported that 8 per cent of catheterized urines obtained under aseptic conditions from 50 healthy women yielded a growth of *B. coli*, but that none exhibited pyuria. Leischman also showed that, without aseptic technic, nine out of ten such urines would yield growth of *B. coli*. His paper emphasizes the danger of contaminating urine specimens with the normal bacterial flora of the urethra, a source of error which has frequently been noted in the literature.³

MATERIAL

Routine cultures of the urine and, in the majority of cases, Addis counts on the urinary sediment were done on 100 women hospitalized in the women's medical ward, clinic service, between October 1939 and April 1940. The cases were consecutive and unselected with the following exceptions. An occasional critically ill or moribund patient was not disturbed. Early in the study a few patients were missed because the routine for obtaining specimens had not been established.

Actually the group is not completely unselected. Clinic patients fall, as a whole, into the lower social and economic brackets. The majority of the patients were sufficiently ill to require hospitalization, but an appreciable number received diagnoses of functional disorders and an occasional individual was brought into the ward more for purposes of demonstration than because of need of hospital care.

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From the Department of Medicine, Stanford University School of Medicine.

- (b) Streptococci. Identified according to their ability to produce hemolysis in blood pour plates. (Brown's classification.¹⁰) Hemolytic streptococci further classified serologically. (Lancefield's classification.^{11, 12})
- (c) Colon-typhoid group. Isolated on Russell's slants. Identified biochemically in broths containing the various sugars. Vosges-Proskauer and Methyl Red tests were resorted to as necessary.

V. *The Addis Count and Interpretation Thereof.* The technic of this test, a measure of the rate of excretion of the various formed elements in the urine, is amply described in Addis's publications^{4, 5} and in the standard texts on laboratory procedure. The normal established by Addis¹³ for the number of pus and renal epithelial cells excreted per 24 hours is two million. This normal was established on a group of healthy young male medical students and we feel that an increase of several million cells per 24 hours cannot be considered abnormal for our type of patient. Addis counts were not done on all patients and were purposely omitted in cases with gross pyuria. Credit must be given to members of the resident staff who performed many of the counts.

VI. *Repeated Cultures.* Reports to the ward of all positive and all doubtful cases included a request for repeated cultures. These were obtained in many cases but, particularly in the early stages of the study, some patients were discharged or transferred before additional cultures could be obtained.

VII. *Information Concerning the Patient.* Complete histories were taken and thorough general examinations were made. Pelvic examinations were done by the resident staff and, in some cases, were confirmed by gynecological consultation.

VIII. *Other Laboratory Procedures.* Pyelograms, renal excretion tests, cystoscopies, etc., were performed by the resident staff. No attempt was made to urge such procedures since one of our purposes was to determine how adequately suspected urinary tract infections are studied routinely.

RESULTS

The 100 cases in the series are analyzed according to the following classification:

- I. Negatives: Cases whose initial urine culture was sterile (including six cases which developed urinary tract infections in the hospital).
- II. Positives (bacilluria plus pyuria): Cases from which a heavy growth of bacteria was obtained on initial urine culture in association with definite increase in the number of pus cells excreted in the 24 h period.
- III. Transient bacilluria.

- IV. Bacilluria without pyuria: Cases presenting a heavy growth of bacteria, but no increase in the excretion of pus cells.
- V. Small numbers of bacteria; pyuria mild or absent.
- VI. Hospital infections.

I. *Negatives.* Cultures of the first catheterized urine specimen from 69 of the 100 patients (69 per cent) were sterile. Six of these patients subsequently developed urinary tract infections while in the hospital. These six, included here for statistical purposes, are discussed in a separate section. A single obvious hospital infection from which no culture was obtained until the acute infection had arisen is omitted from the present section.

Of the 63 cases which did not develop an infection at any time, only a single culture was obtained from 55, two negative cultures were obtained from six and three negative cultures were obtained from two. Of the six cases which developed hospital infections, five had single negative cultures and one had two negative cultures before a positive culture was obtained.

Not a single member of this group gave as a presenting complaint any symptom or group of symptoms referable to the urinary tract. In only two of the cases which did not develop a hospital infection was a diagnosis made of pathological change in the urinary tract, and in both of these the diagnosis was "mild unilateral hydronephrosis" based on pyelograms. A past history was obtained from 68 of the 69 patients in the group. Reference to the urinary tract was completely negative in 29 (42.7 per cent) and was positive in 39 (57.3 per cent). Each of the patients admitting past urinary difficulties enumerated single or multiple symptoms over vague and protracted periods of time; 34 (50 per cent) noted nocturia, alone or in combination, and 13 (19.1 per cent) mentioned frequency or dysuria. Twenty patients (29.4 per cent) described definite episodes of urinary tract disorder; 13 (19.1 per cent), a single attack, and 7 (10.3 per cent), two attacks. These attacks are briefly described in table 2 and are summarized statistically in table 4.

No patient in this group admitted any definite urinary tract disorder relating to the present illness, although 11 (16.2 per cent) connected the onset of single symptoms, such as nocturia or dysuria, with the present illness.

Pelvic examination was performed in 63 of the 69 cases; it was unremarkable in 36 (57.1 per cent), but revealed abnormalities in 26 (42.9 per cent). These abnormalities are summarized in table 5.

Pyuria was present in 11 cases, in 10 of which it seemed to be adequately explained by diagnoses other than urinary tract infection. Pyelograms were made in 12 cases; were normal in four (33.3 per cent) and showed some abnormality in eight (66.7 per cent). Probable explanations for the pyuria in these cases and condensed reports of abnormal pyelograms are summarized in table 2.

TABLE II
Cases Presenting Negative Cultures but Some Positive Findings Referable to the Urinary Tract

Case No.	Past History of Definite Urinary Tract Episode	Presence of Pyuria and Possible Explanation Thereof	Abnormalities Found by Pyelographic Examination
4	1938, urinary retention and lumbar pain. 1939, dysuria, frequency and hematuria, 2 weeks 1934, toxemia of pregnancy		Left upper calyx slightly dilated and has poor drainage
5 7			
9	1923, ulcerated ureter, burning and frequency, 3 months. 1928, uremia with first pregnancy		Left terminal calices irregular, ulcerated? Small functionless left kidney. Right renal pelvis dilated and ulcerated
10	1937, urinary tract infection		Blunted right renal calyces
13	1922 and 1936, urinary tract infection		Bilat. anomalous renal pelvis
14	1939, urinary tract infection		
15			
19	1939, urinary tract infection		
21	1920 and 1923, urinary tract infections		No excretion from right kidney
31			
33		Mycosis fungoides involving bladder. Roentgen-ray therapy	
36		Congenital lues: fever therapy	
39	1925, toxemia pregnancy. 1936, urinary tract infection.	Latent glomerulonephritis	
41	1935, pain rt. flank to groin, chills, fever. 1939, rt. ureter stricture, hydronephrosis	Nephrosclerosis and hypertensive cardiovascular disease	Dilated right renal pelvis
43	1938, urinary tract infection		
49	1939, urinary tract infection		
53	1939, acute pyelonephritis		
56		Chronic glomerulonephritis	
62	1927, urinary tract infection	Chronic glomerulonephritis	
63	1939, cystitis		
65	1934 and 1939, cystitis	Generalized arteriosclerosis	
73		Disseminated lupus erythematosus	
74	1939, cystitis		
80			
81	1939, urinary tract infection	Renal insuff. after sulfathiazole	
84	1930, cystitis	Hematuria after sulfathiazole	
93			
97	1936, cystitis	Unexplained: 13/mill./24 hrs.	
100			Dilated right renal pelvis and ureter, drains well

Comment: The incidence of definite attacks of urinary tract infection in the past history of 69 patients with sterile urines at the time of their present hospital entry (29.4 per cent) confirms the impression that these disorders occur frequently. That one infection is apt to be followed by others is suggested by the high rate of recurrence (35 per cent). We are not impressed by the frequent admission of single symptoms, such as nocturia, frequency or burning, since these may arise from several causes and are highly subjective in character. The common occurrence of pelvic abnormalities (40.3 per cent) is to be expected in a group of women of child-bearing age or older. The relatively high percentage of pyelograms revealing abnormalities (66.7 per cent) is not significant since these are ordinarily not made without a suspicion of anatomical or pathological defect.

II. *Positives (Bacilluria Plus Pyuria)*. Cultures of the first catheterized urine specimen from 19 patients (19 per cent) revealed the growth of a large number of bacterial colonies and Addis counts on the urinary sediments from these patients demonstrated definite pyuria. Histories were obtained from 18 of these cases; seven (38.9 per cent) were completely negative and 11 (61.2 per cent) positive. All of the positives admitted nocturia and nine (50 per cent) vouchsafed some other symptom. Nine patients (50 per cent) described definite attacks of urinary infection in the past. Four patients had had more than one such attack. (Tables 3 and 4.) Four patients (22.2 per cent) admitted recent urinary symptoms, but only two (11.1 per cent) described acute attacks. Only two patients presented themselves because of urinary tract symptoms. (Tables 3 and 4.) Pelvic examination was done on 17 patients; was negative in eight (47.1 per cent) and positive in nine (52.9 per cent). (Tables 3, 4, and 5). Pyelograms were made on five patients; they were negative in two (40 per cent) and positive in three (60 per cent). (Tables 3 and 4.) All 19 cases exhibited significant pyuria, and Addis counts were omitted in those with gross pyuria. Pertinent data for these cases, including bacterial counts, are summarized in table 3.

Comment: It is surprising how few of these patients exhibiting bacilluria and pyuria presented themselves with complaints referable to the urinary tract. We have already criticized the significance of a past history of single or multiple vague urinary symptoms and the irrelevance of such symptoms as regards urinary tract infections is attested by the constancy of their occurrence (table 4). A history of definite episodes of urinary tract disorder was obtained in exactly half of the positive cases and in only 29.4 per cent of the negatives. The rate of recurrence was also about 10 per cent greater in the positives than in the negatives. Few patients admitted urinary symptoms with their present illness and there is no significant variation between the positives and negatives. We had expected the relatively high per cent of pelvic abnormalities in the total series (45.5 per cent), but were surprised at the similarity of the two groups. From our material pelvic changes are not a predisposing factor in urinary tract infections.

Table 8 reveals that 12 of the 19 cases exhibiting bacilluria plus pyuria (63.2 per cent) were treated. Treatment was omitted in three cases because the patient was in the terminal stages of some other disease. Serial cultures were obtained until the urine became sterile in only four cases (21.1 per cent), but four cases were transferred or died before the infection could be cleared. Supplementary urine studies, including pyelograms, were done in only five cases (26.3 per cent).

III. *Transient Bacilluria*. A single case may belong in this category. The pertinent data are summarized in table 3.

Comment: It is unfortunate that any pyuria which may have been due to the bacilluria is masked by the primary disease. This case may have been a low-grade infection which cleared spontaneously.

VI. *Bacilluria without Pyuria*. Three cases exhibited an appreciable growth of organisms on one or more occasions without accompanying pyuria.

Comment: The first and second cases had definite bacilluria confirmed by the growth of the same organisms on a second culture. A careful check of the histories of these two cases revealed no pyuria at any time. We cannot interpret them in any way other than as low-grade urinary tract infections. The third case may have been an example of "transient bacilluria" although a second culture would have been necessary to determine this point.

V. *Small Numbers of Bacteria: Pyuria Mild or Absent*. There were seven cases from whom one or more positive cultures were obtained, but in each of these cultures the number of organisms per c.c. was so few and the pyuria, if present, so slight as to preclude any conclusions. The summaries of cases appear in table 3.

Comment: In several cases there were no repeat cultures and in at least one case a second culture was sterile. These cases cannot be dismissed from consideration since several of them have findings suggestive of urinary tract disease. There had been heavy growths of several organisms during the previous entry of Mrs. C. H. The few staphylococci found in the urine of Mrs. V. C. were found on several occasions and on the last culture the organisms were recovered from both ureters. Several of these cases had severe systemic diseases which may have been predisposing to urinary tract infection.

VI. *Hospital Infections*. There were seven clear-cut cases of urinary tract infection originating while the patient was on the ward. From six of these cases a negative urine culture was obtained prior to the occurrence of the infection; from the seventh no preceding negative culture was obtained. The summaries of cases appear in table 3.

Comment: The possible primary and predisposing causes for the seven hospital infections are summarized in table 6. Six infections followed urinary tract instrumentation or catheterization and the interval between the instrumentation and the appearance of symptoms or the obtaining of a

TABLE
Summary of Pertinent Information Concerning
Cases Exhibiting

No.	Age	Primary Diagnosis	Past History Referable to Urinary Tract	Recent Urinary Tract Symptoms	Pelvis
1	45	Arthritis and septicemia, <i>Staph. albus</i> , (coag. +).	Nocturia and dysuria for years.	None	Normal
2	22	Pyelitis of pregnancy.	None		Pregnant
3	35	Partial bowel obstruction.	Nocturia and difficulty in starting stream for years. Renal abscess drained in 1938.	None	Normal
4	46	Diabetes mellitus, acidosis.	Diurnal frequency for years. Urinary tract infection in 1938.	None	Normal
5	55	Cholelithiasis, urinary tract infection, urethral caruncle.	Frequency and dysuria, 2-3 years. Renal stone removed in 1937.	Diurnal frequency, dysuria, occasional hematuria and pyuria 2-3 years.	Cystocele, rectocele, urethral caruncle.
6	36	Bronchiectasis.	None	None	Normal
7	48	Urinary tract infection.	None	Dysuria, incontinence and difficulty in starting stream.	Normal
8	54	Arteriosclerosis, hypertension.	Right ureteral stone, 1917. Right nephrectomy, 1925. Right ureteral stone demonstrated by roentgen-ray, 1933 and 1937. Right flank and back pain, 1937. Nocturia for years.	None	General relaxation of pelvis, abraded urethral meatus.
9	36	Rheumatoid arthritis.	None	None	Normal
10	27	Acute respiratory infection.	Acute urinary retention, 1927.	None	Normal
11	39	Severe seborrheic dermatitis.	None	None	Normal
12	43	Hyperthyroidism. Entered for thyroidectomy.	Nocturia and occasional dysuria.	None	Cystocele, cervical erosion.
13	80	Myxedema. Multiple nutritional deficiencies.	Nocturia for years. Urinary tract infection, 1937.	None	Senile atrophy pelvis.
14	35	Hypertension. Entered for splachnectomy.	Cystitis with pregnancy, 1924.	Recent nocturia.	Cystocele
15	43	Laennec's cirrhosis, advanced portal obstruction.	Severe frequency.	None	Cystocele
16	73	Coronary occlusion. Chronic cystitis.	Cystitis present since 1935. Nocturia, dysuria.	None	Normal

III

Cases Presenting One or More Positive Cultures
Bacilluria and Pyuria

Results of Urine Cultures and Addis Counts			Remarks
Hosp. day	Organisms isolated (colonies per c.c.)	Pus cells Mill/24 hrs.	
2	<i>B. coli</i> , 20,000,000 and <i>Staph. albus</i> (coag. -), 100,000	75	Constant gross pyuria. No pyelograms. Treated. No further cultures.
1 3 4 7 10	<i>Strept. viridans</i> , 70 and <i>Staph. albus</i> (coag. -), 10 <i>B. coli</i> , 3000 <i>B. coli</i> , 20,000,000 Sterile Sterile	gross	No pyelograms. Onset marked by chills, fever and G.I. upset. Treated.
7 36 42 44 48	<i>B. coli</i> , 10,000,000 <i>B. coli</i> , 20,000,000 <i>B. coli</i> , 10,000,000 Sterile Sterile	34	Laparotomy revealed only "stasis in ileum." <i>B. coli</i> were cultured from both ureters. IV pyelograms revealed small left kidney with normal function. Recurrence 1 mo. later.
3 4 9 17 27 31 39 42	Hem. strept. (Group D), 10,000,000 Hem. strept. (Group D), 10,000,000 <i>B. coli</i> , 1,000,000: Strept. 10,000,000 <i>B. coli</i> , 100,000,000: Strept. in broth <i>B. coli</i> , 100,000,000: Strept. in broth <i>B. coli</i> , 100,000,000: Strept. in broth <i>B. coli</i> , 100,000,000: Strept. in broth Hem. strept. (Group D), 1,000,000	gross	Developed acute retention and hypotonic bladder. Stormy course despite treatment. Pyelograms: functionless left kidney, large poorly functioning right kidney.
2 8	<i>Strept. viridans</i> , 100,000 and <i>B. coli</i> , 1000 <i>Strept. viridans</i> and <i>B. coli</i> , total 200	gross	Treated. No pyelograms or further cultures.
2 9	<i>Staph. albus</i> (coag. -), 10,000,000 <i>Staph. albus</i> (coag. -), 10,000,000	gross	No pyelograms. Treated.
2 7	<i>Staph. albus</i> (coag. -), 1,000,000 and <i>Strept. viridans</i> , 100,000 <i>Staph. albus</i> and <i>Strept. viridans</i> , total 75,000	gross	Had 600-700 c.c. residual. Treated. No pyelograms.
1 2	<i>B. coli</i> , 100,000,000 <i>B. coli</i> , 100,000,000	64	No treatment. No pyelograms. Presumably still has ureteral stone.
4 6 14	Unidentified Strept., 100,000,000 Unidentified Strept., 100,000,000 <i>B. coli</i> , 100,000,000 and Strept. in broth only	60	No pyelograms or further study. Treated.
3 6	<i>B. coli</i> , 1,000,000 Sterile	168	No pyelograms. Treated.
2	<i>B. coli</i> , 30,000	85	No pyelograms or treatment.
2	<i>Staph. albus</i> (coag. -), 100,000,000	9	No pyelograms or treatment.
2	<i>B. coli</i> , 1,000,000	gross	No treatment or pyelograms.
2 6 10 17 20 23 26 36	<i>Staph. albus</i> (coag. -), 16,000 <i>Staph. albus</i> (coag. -), 1,000,000 <i>Staph. albus</i> (coag. -), 65,000 Sterile Sterile Sterile Sterile <i>Staph. albus</i> (coag. -), 1,000,000	258 24 39 14 2	Cystoscopy and retrograde pyelograms revealed a dilated right upper renal calyx with stasis. Splanchnic section done on 29th day. Treated.
3 8 15 22 30	<i>B. coli</i> , 1,000,000 <i>B. coli</i> , 3,000,000 <i>B. coli</i> , 10,000,000 <i>B. coli</i> , 500,000,000 <i>B. coli</i> , 25,000,000	gross	No treatment and no further studies.
2	Gram negative bacillus giving sugar reactions of paratyphoid group but serologically unidentifiable, 189 mill.	45	Persistent UTI since 1935 had been resistant to all sorts of therapy. Died on 5th hosp. day.

TABLE III

No.	Age	Primary Diagnosis	Past History Referable to Urinary Tract	Recent Urinary Tract Symptoms	Pelvis
17	34	Acute prostatitis and Laennec's	None	None	Normal
18	55	Arthritis Staph. r.	None	Nocturia and frequency.	Senile changes.
19	65	Urinary tract infection, acute.	Hematuria, dysuria, frequency as a child. Acute urinary tract infections, 1922, 1934, 1935, 1936, 1937, 1938.	Frequency and burning, 5 days.	Normal

Case No.

1	40	Disseminated lupus erythematosus.	Back and flank pain with pyuria 15 years ago.	None	Normal
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Cases Exhibiting

1	43	Hypertension	Nocturia for years.	None	Cervical erosion.
2	45	Hypertension. Urinary tract infection.	Low back pain and "gravel in urine" 15 years ago.	Lower abdominal pain, burning, urgency and frequency, 3 months.	Bartholin cyst.
3	59	Carcinoma, stomach.	None	None	Normal

Cases Exhibiting Growth of Few

1	64	Coronary occlusion.	Nocturia for yrs.	None	Normal
2	41	Rheumatoid arthritis.	None	None	Eroded cervix.
3	60	Arteriosclerosis. Hypertension.	Nocturia for yrs.	None	Urethra polyp.
4	49	Hypertension	Acute urinary tract infection, 1915.	None	Cystocele
5	56	Chr. hepatitis.	Nocturia for yrs.	None	Normal
6	25	Periarteritis nodosa.	July 1939 urinary tract infection with <i>B. pyocyaneus</i> 5 wks. <i>B. coli</i> 1 month.	None	Normal
7	43	Partial bowel obstruction. Chronic cystitis.	Nocturia, dysuria and frequency for years.	None	Cystocele. Rectocele.

Hospital

1	36	Hypertension. Chronic pyelonephritis.	Severe pyelonephritis, 1922 and 1936.	Following nephrectomy temp. elevated to 39° C.	Normal
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tion can be gained from a study of the literature. . . . Recently, the only thorough studies have been made on isolated species, the identification in large series being made on simple and conservative lines. Since many of the strains isolated do not correspond exactly with common organisms, it is obvious that more careful investigations should be made." We feel that this statement is as true today as it was 15 years ago.

That *B. coli* is the organism most frequently involved in urinary tract infections is in agreement with the majority of papers on the subject. However, in Young's series the Gram positive cocci were isolated more frequently than were the Gram negative rods. All of the staphylococci in our series were producers of white pigment and all were coagulase negative. This finding raises the question of the relation of bacterial virulence to the production of urinary tract infections. Young pointed out that the color of the pigment produced by a staphylococcus is no criterion of its pathogenicity and the majority of staphylococci isolated in his series were white pigment producers. Schulte has suggested the use of the coagulase test for determining the virulence of staphylococci and of animal inoculation for determining the virulence of all organisms recovered from the urinary tract. The failure to prove an organism virulent by these methods would not necessarily indicate an inability to produce urinary tract disease. Some ordinarily non-pathogenic bacteria are invasive in the presence of an obstruction or other pathological change in the tract.

The significance of streptococci in the urinary tract is debated. Young states that the organisms are commonly found in mixed culture and are frequently isolated from the urine of patients with no urinary symptoms. Lancefield¹¹ found that, with a single exception, only hemolytic streptococci of her Group A produced disease in man. Subsequent studies^{15, 16} have implicated streptococci of Groups B and G in human infections and it is conceivable that under special circumstances members of other groups might produce disease.

Four cases in this series exhibited a secondary invasion or overgrowth by *B. coli* after an initial culture has been positive for only Gram positive cocci. Is it possible that *B. coli* is usually a secondary invader and that its presence in pure culture indicates a complete eradication of other organisms by its growth?

We feel that these urinary tract infections are worthy of more exacting and protracted study. The probable fundamental importance of the urinary tract to general health and to the diseases of later life is becoming more and more apparent. Schroeder and Steele¹⁷ have recently found a surprisingly high incidence of abnormalities of the renal pelves and ureters in patients with hypertension. Since the incidence of such changes is high in the general population these findings may be incidental or they may indicate an etiologic relationship between the urinary tract pathology and hypertension.

CONCLUSIONS

1. Cultures and Addis counts were performed on the catheterized urine from 100 unselected cases on the women's medical ward. The initial cultures from 69 women were sterile. Nineteen cases exhibited bacilluria and pyuria; three cases, bacilluria without pyuria; seven cases, small numbers of organisms without appreciable pyuria. One case had, apparently, a transient bacilluria. Seven cases developed urinary tract infections during their hospital sojourn.

2. The high incidence of positive urine cultures in the population of a women's medical ward and the numerous definite attacks of urinary disorders in the past history obtained from these women suggest that urinary tract infections are more ubiquitous than has hitherto been emphasized.

3. If recent studies relating the occurrence of permanent renal damage and vascular changes to urinary tract abnormalities are confirmed, urinary tract infections deserve more careful study and treatment.

4. Since the history and physical examination of patients with urinary tract infections may so often be non-contributory, the diagnosis depends upon quantitative bacterial counts and controlled studies of the urinary sediment.

5. We suggest the following mode of approach to these cases: (a) routine Addis counts; (b) the use of only catheterized urine specimens for culture; (c) repeated quantitative cultures of the urine before the institution of treatment and periodically thereafter until the urine is sterile; (d) energetic treatment according to a definite plan; (e) supplementary investigation of the urinary tract after the urine has been sterilized; and (f) adequate follow-up for the discovery of recurrent infections and for the correction of anatomical abnormalities.

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BIBLIOGRAPHY

1. (a) WEISS, S., and PARKER, F., JR.: Pyelonephritis; its relation to vascular lesions and to arterial hypertension, *Medicine*, 1939, xviii, 221-315.
(b) LONGCOPE, W. T.: Chronic bilateral pyelonephritis; its origin and its association with hypertension, *Ann. Int. Med.*, 1937, xi, 149.
2. LEISCHMAN, A. W. D.: *Bacillus coli* infection of the urinary tract; its relation to bowel function, *Lancet*, 1939, ii, 971.
3. (a) SAVOR (1899) and ROUSING (1910) cited in YOUNG, H. H.: *Practice of urology*, Vol. I, 1926.
(b) SCHULTE, T. L.: Newer methods in the study of the bacteriology of urinary tract infections, *Proc. Staff Meet. Mayo Clinic*, 1939, xiv, 249-254.
4. ADDIS, T.: A clinical classification of Bright's disease, *Jr. Am. Med. Assoc.*, 1925, lxxxv, 163.
5. ADDIS, T.: Rapid quantitative laboratory methods for use in a doctor's office. *Annual Post-Graduate Course, Stanford University School of Medicine*, September 1938.
6. DU ROCHMONT, DE MESNIL: *Zur Pathologie der Blasenentzündungen*, Berlin, 1896.
7. SCHULTE, T.: Bacteroides and anaerobic streptococci in infections of the urinary tract; report of a case, *Proc. Staff Meet. Mayo Clinic*, 1939, xiv, 536-538.

8. BLAIR, J. E.: The pathogenic staphylococci, *Bact. Rev.*, 1939, iii, 97-146.
9. CRUICKSHANK, R.: Staphylocoagulase, *Jr. Path. and Bact.*, 1937, xlv, 295-303.
10. BROWN, J. H.: The use of blood agar for the study of streptococci, *Monographs Rockefeller Institute Med. Res.*, No. 9, New York, 1919.
11. LANCEFIELD, R. C.: Serological differentiation of human and other groups of hemolytic streptococci, *Jr. Exper. Med.*, 1933, lvii, 571-595.
12. LANCEFIELD, R. C.: Micro-precipitin technique for classifying hemolytic streptococci and improved methods for producing antisera, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxviii, 473-478.
13. ADDIS, T.: The number of formed elements in the urinary sediment of normal individuals, *Jr. Clin. Invest.*, 1926, ii, 409-415.
14. YOUNG, H. H.: The practice of urology, 1, pp. 90-132, 1926.
15. FRY, R. M.: Fatal infections by hemolytic streptococcus Group B, *Lancet*, 1938, i, 199.
16. RANTZ, L. A.: Suppurative arthritis due to a hemolytic streptococcus of the Lancefield Group B: a case report, *ANN. INT. MED.*, 1940, xiii, 1744-1747.
17. HROEDER, H. A., and STEELE, J. M.: Abnormalities of the urinary tract in essential hypertension, *Proc. Soc. Exper. Biol. and Med.*, 1938, xxxix, 107.

INTERMITTENT LIMPING—INTERMITTENT CLAUDICATION; THEIR DIFFER- ENTIAL DIAGNOSIS *

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THE symptom "intermittent limping" has become so associated with intermittent claudication that clinically, to many, the terms have become almost synonymous. The term "intermittent limping" describes a sequence of events in which the patient finds repeatedly that, after walking a few blocks, he must come to a complete halt because of a cramp-like pain or sense of exhaustion in one or both legs. The first physician consulted usually refers the patient complaining chiefly of this symptom to a colleague particularly interested in peripheral vascular diseases. However, the complaint is frequently due to non-vascular causes.

An analysis of all such cases referred to us shows that often a closure of the peripheral vessels is found. At times more than one cause for the intermittent limping can be present, an endarteritis obliterans being only one of them, and at other times no arterial involvement can be disclosed. On this account, we believed that a review of the vascular and non-vascular causes for intermittent limping as found in our clinic, would lend emphasis to several points we believe helpful in differential diagnosis.

Locomotion in the adult is dependent upon a well balanced alignment of the osseous system and mobility of the articular surfaces. The musculature related to these bones and actuating the motion of their joints by its rhythmic contraction and relaxation, produces locomotion. The actuation and direction of this mechanism is dependent upon an intact and balanced nervous system. The need for increased nutrition to these parts while walking is at its height, requires a patent and elastic vascular system. A breakdown in the efficiency of any one of these three systems will interfere with the successful performance of the act of walking. A clonic contraction of the extensor muscles of the leg is an extremely effective method of bringing about and forcing such a rest period on the ambitious patient. The embarrassed part must rest to recuperate. A halting walk or limping follows.

Admittedly then, the symptom of intermittent limping alone is insufficient to make a diagnosis of obliterative vascular disease. The other systems may be at fault and a complete medical examination must be made to help clear up the question. If the findings are conclusive, their proper evaluation must be attempted; if indefinite, due to an early pathologic condition, the problem remains obscure. This is especially true if there is more than one cause for the intermittent limping. Our observations on the va-

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rious causes for this symptom are discussed under their respective anatomical systems and form the basis of this report.

Muscle and bone imbalance in the leg and foot is a frequent cause of intermittent limping. Because of its general prevalence it is often present in those suffering with vascular diseases. This disturbance is most frequently produced by a shortened achilles tendon and gastrocnemius muscle. It prevents full acute dorsi-flexion of the ankle. This condition may be present on a congenital basis or acquired, as in women by the use of high heels. The stress produced by the inability to dorsi-flex the foot while walking causes a severe spasm of the shortened calf muscles. An imbalance of the metatarsal heads, which the gastrocnemius and soleus muscle use for a fulcrum in the forward motion of the leg, will strain the muscles and cause limping. Evidence of such a condition is found in the presence of uneven callus formations and roentgen-ray evidence of a short first metatarsal.

It is remarkable how patients obsessed for a long time with a fear of amputation, based on an improper diagnosis, will be relieved in 24 hours by simple "calf stretching" exercises. A recently observed case illustrates this very well. This patient, because of his 68 years and the rigidity of his vessels, and in spite of his normal oscillometric readings, had been considered to be suffering from a vascular disorder. Previous treatment for this had made matters worse. On examination, however, a marked shortening of the tendo achilles on both sides was found. He was an actor and had tap-danced on his toes for many years. Because of his failure to find work and having had to walk about town for months seeking employment, his gastrocnemius muscle had been overstretched and thrown into a clonic spasm. Calf stretching exercises were prescribed and after a week the intermittent limping was cleared up. The patient recognized the mechanism immediately and volunteered the information that for years he had done these exercises unconsciously because he found that they helped him in his work.

Another instance of this was seen in a woman who had been admitted to a local hospital for cardiac failure and auricular fibrillation. While confined to bed she developed a severe cramp-like pain in her right leg. The pulses in both dorsalis pedis arteries were difficult to palpate and the oscillometric readings were low. In auricular fibrillation it is frequently difficult to evaluate the oscillometric findings because of the wide fluctuations in the timing and the force of the pulse. However, it was thought that an embolus from the auricle had lodged in the vessels of her leg, not an unusual occurrence in auricular fibrillation. Hearing this discussed at ward rounds, the patient immediately developed a severe anxiety neurosis. She became hysterical and had to be sent out of the hospital. When seen in consultation at home, the absence of active dorsi-flexion at the ankle gave the appearance of a foot drop. However, passive motion also was found to be impossible because of an extreme contraction of the gastrocnemius and its tendon. It took a great deal of time and persuasion to make the patient understand that she had no obliterative vascular disease and would not lose her leg. All that she re-

quired was elevation of her heel so that the shortened muscle could not be pulled into a clonic spasm. The intermittent limping ceased.

For the proper coördination of the activities, muscles work in groups whose contractions are actuated by a single large nerve. A peripheral nerve lesion can therefore disable an entire group partially or completely, depending upon the degree of the injury. A group of muscles burdened with the work which should be carried on by its atonic neighbor will soon tire. Whatever the chemical agent generated by this exhaustion may be, the muscles become clonically spastic and locomotion is at once halted. Such a situation was found in a patient who was referred to us because it was thought she had claudication. On examination, instead of a diseased vascular system, the adductor muscles of the thigh were found to be paralyzed. The obturator nerve had become enmeshed and crushed by a malignant tumor in her pelvis. The vascular system was not involved. The case was one of intermittent limping because of the unequal distribution of work resulting from the failure of the adductor group to contribute its share.

In locomotion there is a synchronized contraction and relaxation of muscle tissue making for smooth progress. If the basal tonus of a resting calf muscle is increased by a pathologic condition and the stress of ordinary walking is then added to it, the summation of their energies will result in a clonic spasm of the overworked muscles. Such a hypertonicity can be brought about by the chemical disturbances causing tetany or the pathological changes present in extra-pyramidal and posterolateral column lesions. An illustration of such a chemical derangement recently presented itself in a patient whose complaint was intermittent limping, cold feet and edema of the legs. The arteries were not palpable and the oscillometric readings were low. Response to vascular therapy was poor, however, and the diagnosis was not clear. While under observation, a routine examination of the blood electrolyte partition was made for the explanation of vague symptoms. A low serum calcium was found. Further questioning and examination brought out the presence of a non-tropical sprue as a cause for the steatorrhea and loss of calcium. The coincident edema of the legs due to a low serum protein accounted for the difficulty in finding the vessels and the lowered oscillometric readings. The poor mental caliber of the patient which may have been due to a vitamin deficiency did not facilitate the medical examination. After appropriate treatment the edema cleared, the serum calcium rose and the walking tolerance was greatly increased as the tetany cleared.

The degenerative diseases which involve the extrapyramidal system and the lateral columns of the spinal cord have been found to be a frequent cause of intermittent limping. Of the cases we see these offer the most interesting problems in differential diagnosis. It should be apparent that the neurological signs are not advanced in character or the patient could not have been referred for intermittent claudication. The motor cells at the base of the brain in the hypothalamus and the neighboring nuclei produce stimuli which reënforce rather than initiate motion. Their involvement by a disease

process produces in the mild case, simply an increase in muscle tone and in the advanced case, a very marked rigidity of the muscles. A case which falls into this group was seen recently. This patient had a history of stomach trouble and intermittent limping for three years. On examination, his peripheral arteries were not palpable but his oscillometric readings were normal. His arteries probably ran an abnormal course. Further examination disclosed a bilateral ankle clonus, hyperactive knee jerks and slight sensory changes, pointing to extra-pyramidal lesion. The cause of his intermittent limping lay in the hypertonus emanating from the diseased basal cell nuclei. In this case, an old cranial trauma was probably the underlying factor.

Because their chief complaint is intermittent claudication we are frequently asked to see patients who have spinal cord disease. These patients have a diffuse combined degeneration of the spinal cord known as posterolateral sclerosis. This is an intrinsic degenerative disease of middle age which may appear coincidentally with sclerotic changes in the peripheral vascular system, a combination which makes for great uncertainty in differential diagnosis. In addition to the hyperactive reflexes, the presence of the Babinski sign, ankle clonus and loss of position sense, there is a hypertonicity of the musculature which, in cases of extreme involvement, is characterized by what is called the scissors gait. It is this increased tonus which, when the patient begins to walk, throws the calf muscles into a clonic spasm and brings him to a stop. Such a patient was recently referred to us on account of intermittent claudication. The lowered oscillometric readings seemed at first to confirm our impression that the complaint was entirely due to a partial arterial obstruction. Complete examination, however, revealed sufficiently characteristic signs to warrant an additional diagnosis of posterolateral disease. No free HCl after a histamine test meal was found. Treatment was at first directed to the vascular system but was without effect. After a change to a high vitamin diet and liver extract parenterally, the progress of the disease was at least limited and a trend to improvement was started.

Syringomyelia, with intermittent limping as the chief complaint, has also been encountered. It mimics the intermittent claudication of endarteritis obliterans and the differentiation is rendered even more difficult because the patient states that his leg feels cold. As the clinical picture becomes clearer, it becomes apparent that because of the loss of temperature sense, the skin of his affected leg is not conscious of its own surface heat, whereas the skin of the unaffected leg is conscious of it.

Intermittent limping by a patient who presents a pale leg with evident areas of soft tissue destruction and absent vessels is not a problem in diagnosis. However, in this paper we are concerned with the border line case. It is irrelevant here whether the condition is one of endarteritis obliterans due to a non-specific infection or to arteriosclerosis. The question is whether there is a patent arterial system and if not, is it so inadequate as to cause intermittent limping. The first and simplest procedure is to feel for the

superficial arterial pulses at the ankle; in the popliteal space and at the femoral ring. If absent, one must wonder if it is merely too difficult to find. The dorsalis pedis artery is very frequently not present on the dorsum of the foot. The posterior tibial artery may be impalpable behind a prominent malleolus often found in people with squat feet. Edema of the lower third of the leg also may hide the two vessels. The popliteal artery, usually located just inside the mesial tendon of the gastrocnemius muscle, is frequently buried in fat or ephemerally felt in the patient who just cannot relax. One can easily surmise that palpation alone is not enough, but the absence of any of these pulses is certainly provocative to further study.

The color of the skin, if the superficial circulation is patent, is dependent upon an adequate arterial blood supply. Therefore, it may be made use of in finding out whether the arteries are adequate. The leg is elevated, the foot flexed several times, rendering the skin colorless. Lowering the leg to a dependent position would normally cause a prompt return of the pink color. If there is a definite delay, the arterial blood supply is insufficient. However, it is also delayed when the skin is cool. So for the test to be of value, the skin of the leg must be warmed in a whirlpool bath or by heating one of the other extremities not being studied. The anxiety states of some people induce so resistant a vasoconstrictive reflex, that it takes a long time to dilate the subpapillary plexus. The test is then useless for practical purposes.

The oscillometer measures the height of the pulsation of an artery. Inasmuch as some of the factors which contribute to the makeup of the pulsation, namely, the mass of blood circulating, the velocity of the stream and the tonus of the vascular system, are the same for points equi-distant from the left ventricle, the variations in the readings of the oscillometer should give information concerning the structure of the artery underneath its cuffs. The membrana elastica, the medial wall and the diameter of its lumen will be the only factors under these circumstances. The inability of these structures to yield to the systolic onrush of blood and to permit its free passage will result in a low pulsation and a low oscillometric reading. If only one side is affected, then the uninvolved side may be used as a control. If both sides are involved, then the standard for comparison must be that which experience has established for the particular instrument used. In our clinic we have established for the lower extremities the standard of *three* for the lower third, *five* for the upper third of the leg and *eight* for the lower thigh. This instrument has been found to be of great importance in the study of a vascular problem.

The environmental and body temperatures will affect the oscillometer reading by varying the neuromuscular tonus of the arterial wall. If the environment is cool, the reading is lowered because chilling contracts the lumen of the artery. A whirlpool bath at 105° F. for 10 minutes will abolish such a spasm. When there is a large difference in the oscillometric readings on both sides, and the lower reading is still within the normal limits, it must be

assumed, especially if there are symptoms present, that there is involvement of the questionable artery until proved otherwise. This situation is not infrequently found and only after prolonged observation can a final conclusion be reached.

There are other methods of examination but these are more confirmatory in character and useful in determining not only the level of involvement, but also the prognosis. In this field, we use the roentgen-rays to search for calcification in the vessels, and the skin temperature before and after warming or nerve block, the histamine wheal and the exhaustion or claudication time after muscle stimulation for further information. An equally normal oscilometric reading on both legs is the most dependable sign of a competent peripheral vascular system.

Great mental strain is produced in a patient when he is informed that he has peripheral vascular disease. He immediately sees an amputation in the offing. Great care and restraint must be exercised lest unnecessary anguish be caused such a sufferer who comes in for intermittent limping not caused by claudication.

The complaint "intermittent limping" is a challenge to careful differential diagnosis. It has been shown that especial attention should be paid not only to studies of the peripheral vascular system but also to the orthopedic and neurological systems. Examples of these problems have been drawn from our experience in peripheral vascular studies on patients referred to us for consultation. A growing consciousness of the problem has increased the percentage of cases whose complaint was really intermittent limping and not the intermittent claudication due to peripheral vascular disease.

PNEUMONIA AS IT MAY AFFECT YOUNG ADULTS: 300 CONSECUTIVE CASES AMONG STUDENTS AT THE UNIVERSITY OF WISCONSIN*

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THERE is in evidence a growing appreciation of the fact that pneumonia is far from being a disease sharply limited within the confines of definite clinical specification. That pneumonia may be caused by a considerable variety of bacterial agents is well known, each organism endowed with different degrees of virulence, which, further, may fluctuate from time to time. So, also, is recognized the modification of symptoms and prognosis possible by quantitative pulmonary and hemic involvement, as well as by such qualitative factors as age, physical condition and individual resistance in the patient. As McKinlay⁶ remarks, Bullowa and Wilcox¹ have well summed up the situation when they stress that the endemic pneumonias are a *series* of diseases, varying as to their occurrence from year to year and from month to month, and differing in respect to the age of the patient, incidence, mortality, tendency to invade the blood stream, and other characters.

Most papers on the subject of pneumonia concern themselves with the pneumococcal forms, usually depicting severe lobar involvement with a very high mortality, and, in recent years, proceeding to a discussion of the improved results obtainable through serotherapy and chemotherapy. Again, bronchopneumonia in children, the aged, the debilitated and the post-operative patient has been rather thoroughly described, as has now the aspiration pneumonia due to oils. Only a few writers have presented data with regard to pneumonia in relatively healthy young subjects. The majority of these last presentations have originated in college and university student health sources, probably due to the unparalleled opportunity possessed by clinicians in this field of medicine to observe impressive numbers of instances of acute respiratory illness, among which, inevitably, cases of pneumonia will be discovered.

We have been impressed with an apparent confusion in the minds of some of those who have written about student-age pneumonia, though it may have been rather a reluctance on their part to resort to the prevailing terminology and narrow standardization fashionable in the pneumonia field. At any rate, it has been manifested by a tendency to favor, almost apologetically, a nomenclature employing such terms as "atypical bronchopneumonia," "pneumonitis," and the like. It seems to us that there is nothing particularly atypical about the cases of pneumonia commonly observed in young adults

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such as we propose to describe among our university students. Instead, we feel there is a need to revise previous classifications and descriptions of so-called "typical" pneumonia, so as to guarantee inclusion of a very prevalent type of case.

At the University of Wisconsin, where the enrollment ranged from 7,500 to 10,000 during the regular session, and from 3,500 to 5,500 during the summer session, there occurred 368 cases of pneumonia in the eight years, 1931-1939. Each year of record began July 1, and ended June 30, of the following calendar year. The present study analyzes the data collected from the medical records of the first 300 consecutive cases in this series. All the patients were university students, referred to the Student Infirmary, and there cared for by physicians of the Department of Student Health, assisted on many occasions by physicians from the staff of the State of Wisconsin General Hospital.

INCIDENCE AND EPIDEMIOLOGY

From mid-August until mid-September, when the University was not in session, and similarly during the Christmas and Spring recesses, there were virtually no students on the campus. If this be borne in mind, it will be seen in table 1 that pneumonia was encountered in every month except

TABLE I
Incidence of Pneumonia by Month and Year

Academic Year	July	1st $\frac{1}{2}$ Aug.	2nd $\frac{1}{2}$ Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	Total
1931-32	0	0	0	0	0	0	0	14	0	0	1	0	15
1932-33	0	0	1	1	5	6	5	2	0	0	0	0	20
1933-34	1	0	0	2	2	3	4	3	0	2	0	1	18
1934-35	1	0	0	3	3	5	5	1	6	3	4	8	39
1935-36	3	0	1	7	8	2	6	6	7	7	2	0	49
1936-37	1	0	2	5	9	6	4	0	1	2	1	0	31
1937-38	1	0	1	7	14	4	6	12	11	4	7	1	68
1938-39	2	0	4	26	38	22	8	9	13	3	1	2	128
Total	9	0	9	51	79	48	38	47	38	21	16	12	368*

* The first 300 consecutive cases are reported in this study.

August. The disease tended to make its appearance in significant volume early in the autumn term, slackening off somewhat by Christmas, and showing a second surge upward after classes were resumed in January, this subsiding as spring advanced. The academic year of 1931-32 was the sparsest in pneumonia, 14 of the total 15 cases occurring closely grouped in February. In fact, the first three years of this study showed a relatively low level of incidence of pneumonia and of all respiratory tract infections in general, while there was a gradual, steady rise in the figures for the last five years of the period, culminating in totals of 68 cases of pneumonia in 1937-38 and 128 cases in 1938-39.

A glance at figure 1 informs us that peaks in respiratory illness other than pneumonia were very closely followed in direction by the curve tracing pneumonia levels. Totals in all categories reached their tops in the year 1938-39. We were not able to plot any consistent or significant relationship between the incidence of grippé-like affections on the one hand, and of pneumonia or other respiratory maladies on the other. To us it seemed that this entity pursued a pattern all of its own, its outbreaks being annual, though not predictable as to exact seasonal occurrence, and with occasional moderate epi-

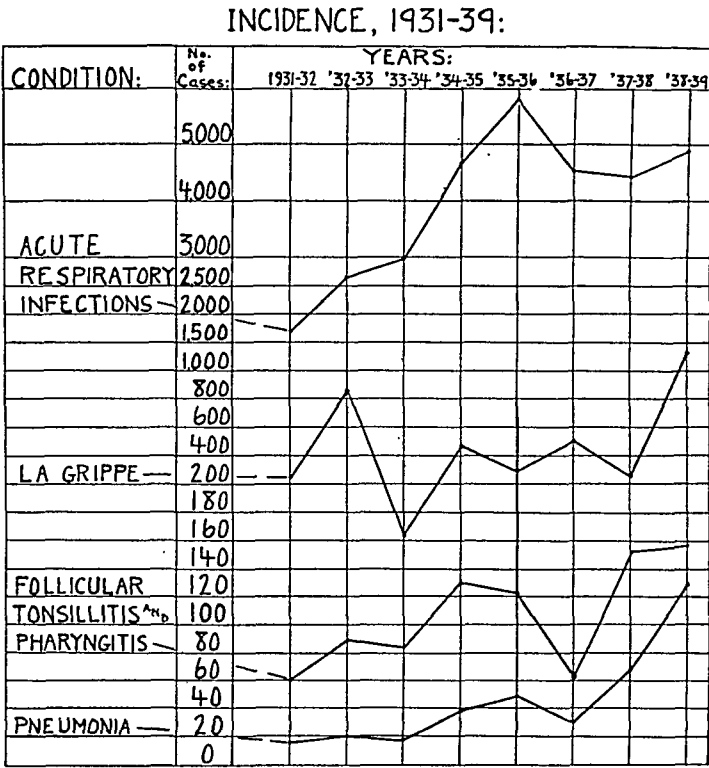


FIG. 1.

demic proportions, as in 1932-33 and 1938-39. We were unable to duplicate in our practice the experience of McKinlay et al.,⁶ who reported that in years when influenza showed a rise, follicular tonsillitis had fallen off.

As would be anticipated, the vast majority of our patients were between the ages of 17 and 26 years, 280 being in that category. Two were 16 years old, 12 between 27 and 32, one was 38, three 39, one 45 and one 49. Average age for the group was 20.9 years.

There were 80 women and 220 men in the series. All were white but one, a negro. It may seem irrelevant, but we gained the impression, as we cared for the patients, that a rather large proportion were Jewish. Final analysis revealed that 56 individuals, or 19 per cent, were Jews, in a student

community where the percentage ran hardly that high, being approximately 12 per cent.

The immediately recent medical history of our patients showed, as will be related subsequently, a large number of acute respiratory illnesses, out of which subjective pulmonary symptoms developed, or because of which the patients finally sought medical advice and care, and were then found to have evidence of pneumonia or to be in the process of developing it.

However, it is interesting to note that the truly past medical history revealed only 155 individuals with a completely favorable and uneventful back-

TABLE II
Past Medical History of Pneumonia Patients

		No. Cases
Group I—Reporting good health:		
Satisfactory, uneventful past medical history		146
Past medical history "fair"		9
Total		155
Group II—Reporting one or more significant health impairments previously:		
Total		145
		No. Instances
Frequent acute upper respiratory infections		73
Previous attacks of pneumonia		36
1	Previous attack	31
2	" attacks	1
3	" "	4
Chronic paranasal sinusitis		22
Chronic rheumatic heart disease		8
Bronchial asthma		7
Chronic bronchitis		7
Recovery from recent acute illness		6
Chronic tonsillitis		5
Generally poor health, not itemized		5
Chronic bronchiectasis		4
Malnutrition		4
Previous acute pleurisy		3
Seasonal pollenosis, severe		3
Chronic otitis media		2
Diabetes mellitus		1
Pulmonary tuberculosis, minimal, arrested		1

ground of good or fair health. No less than 145 young men and women, practically half the entire group, reported previous significant sickness or suffered from chronic conditions which operated as further health hazards. The most frequent of these handicapping conditions (table 2) was that of recurrent, usually severe, acute upper respiratory tract infection, while chronic paranasal sinusitis and other chronic tonsillar or respiratory ailments such as asthma, bronchiectasis or bronchitis added up to an impressive total. There were 36 students who had experienced previous attacks of pneumonia, five having survived multiple episodes. Chronic rheumatic heart disease was observed in eight patients.

As Locke ⁵ has pointed out in experiments on animals, high "fitness" ratings increase the ability to survive pneumococcus infections, and low ratings have the opposite effect. This being so, it seems probable that the same principle would apply to pneumonia caused by other organisms. One might be led also to expect a lower infection rate among "fit" individuals in the first place.

Schwartz ¹⁰ collected a series of 654 pneumonia cases in which over half gave histories of upper respiratory infection prior to the onset of the disease, and more than one-third of his series presented evidence of important chronic lesions. McKinlay and his coworkers ⁶ report as high as 74 per cent with preceding respiratory tract maladies in their patients with bronchopneumonia, whereas in Murray's ⁸ experience less than half had had a cold within three weeks of the diagnosis of pneumonia.

TABLE III
Anatomical Distribution of Pneumonia

A. 244 cases with single lobe involvement:

Lobe	Broncho-pneumonia	Lobar pneumonia	Lobe	Broncho-pneumonia	Lobar pneumonia
Right upper	13	1	Left upper	8	0
Right middle	5	1	Left lower	109	3
Right lower	100	4			
Total	118	6	Total	117	3

B. 56 cases with multiple lobe involvement:

Lobe	Broncho-pneumonia	Lobar pneumonia	Lobe	Broncho-pneumonia	Lobar pneumonia
Right upper	24	0	Left upper	11	2
Right middle	16	1	Left lower	30	2
Right lower	31	1			
Total	71	2	Total	41	4

C. Cases classed as bronchopneumonia	289
" " " lobar pneumonia	11
Total	300

CLINICAL CONSIDERATIONS

It will be seen from table 3 that 289 of our cases were classed as bronchopneumonia, only 11 other cases being diagnosed as lobar in nature. It was our purpose in this communication to report all the pneumonia that occurred on the campus during the time selected for scrutiny, and not to limit ourselves to discussion of any special group, anatomic or etiologic. Generally speaking, the cases here reported were of a relatively milder type than most series reaching the literature from large urban centers and General Hospital practice. Therefore, the term "lobar" as applied to 11 of our patients is

based more on roentgenologic and physical findings than on any currently popular clinical concept of what constitutes lobar pneumonia. However, not all our pneumonias were mild, there being 11 deaths during the eight years, a mortality of 3.6 per cent, while many of those who recovered experienced a very severe illness throughout. Nine of the fatalities were doubtless traceable directly to the pulmonary disease, two others partially due to overwhelming illness co-existing elsewhere. During the time that we lost 11 patients by pneumonia, the total deaths at the Infirmary were 24, so that pneumonia, while a relatively mild disease in the mass, was the greatest single cause of death on the campus, accounting for almost half of all student fatalities, and well in excess of half of those deaths not due to accidents.

Table 4 lists the diagnoses made at the entrance of the patients to the Infirmary. The procedure was to refer the cases either from an office visit at the Clinic or from a house visit at the student's room. They were first

TABLE IV
Diagnoses as Recorded at Entrance to Hospital

	No. Cases
Group I—Pneumonia suspected by examining physician:	
Bronchopneumonia	43
" with la grippe	36
" acute rhinopharyngitis	31
" acute bronchitis	29
" , resolving	8
" with diaphragmatic pleurisy	3
" chronic bronchiectasis	2
" Vincent's gingivitis	1
" acute tonsillitis	1
" chronic sinusitis	1
" scarlet fever	1
" bronchial asthma	1
" pleural effusion	1
Lobar pneumonia	8
	166
Group II—Pneumonia not suspected by examining physician:	
Predominantly "la grippe" type of diagnosis	93
" "acute upper respiratory" type	20
" "acute lower respiratory" type	11
	124
Group III—Pneumonia developed as a complication:	
Tonsillectomy	1
Repair of hydronephrosis	1
Cellulitis of head	1
Acute appendicitis; appendectomy	1
Furunculosis	1
Varicella	1
Acute follicular tonsillitis	1
Acute rheumatic fever	1
Acute purulent pericarditis	1
Subacute bacterial endocarditis	1
	10
	300

seen immediately upon admission by an interne, then by a resident, and finally by a staff physician attached to the Department of Student Health. Very ill cases were often examined by these doctors working in a group. Any diagnosis recorded by any of the medical attendants during the first day of the patient's stay in hospital or following his development of symptoms suggesting complication or exacerbation of illness for which he might already have been under treatment, was noted as an entrance diagnosis and will be found in Group I. It is observed that only 166 cases, or 55 per cent, gave a history or provided physical findings sufficiently positive to justify a provisional diagnosis of pneumonia at that stage. In Group II, 124 individuals were diagnosed as having *la grippe*, "influenza," or some form of respiratory tract infection short of pneumonia. In other words, pneumonia, if present at that juncture, was overlooked or was not ascertainable by routine methods. Ten cases in Group III are known to have been free of pneumonia on admission, but developed it while in the hospital for other quite distinct illnesses. Thus, we feel amply fortified by facts when we state that pneumonia in healthy young people is not simple or easy to diagnose at its onset, even when under the almost ideal conditions of closely checked physical examination obtaining in a well-staffed, modern hospital.

Smith,¹² in contrasting the dramatic onset of typical lobar pneumonia with that of typical bronchopneumonia, refers to the latter as "slithering into the picture of an ordinary bronchitis. . . ." The definitely insidious onset in many of our own cases is supported by entrance histories which inform us that only eight patients entered the Infirmary during the initial 24 hours of their illness. We had 169 cases, or 56 per cent of the series, who managed to report before they had been sick four days, but 68 others had been sick for five to 10 days before seeking medical assistance, and 23 others, presumably walking cases of pneumonia, had been ill or felt poorly for varying periods ranging from 12 to 28 days. During this time, they, like their short-sighted fellow patients, had tried to take care of themselves or had neglected their symptoms entirely. Finally, there were 10 patients whose pneumonia arrived to complicate unrelated conditions.

The clinical picture described in detail by various authors, notably by Murray,⁸ by Miller and Hayes,⁷ and by Smiley and his aides,¹¹ was well substantiated by our cases as well as by the figures just quoted. Generally the patient had felt unwell for a few days, noticing headache, usually frontal in type, general malaise, weakness and anorexia, backache, pains in the legs, cough, feverishness, occasionally mild chills, and frequently those coryzal or catarrhal symptoms customarily associated with a common "cold." Sudden, dramatic, explosive onset was a rare occurrence reserved to a few cases very ill at entrance. We have listed in order of their frequency the commonest chief complaints at entrance (table 5), and the commonest symptoms amassed from all symptoms reported in the history of the present illness as recorded by the internes. Cough heads both tabulations, though it is not a

TABLE V
Subjective Symptomatology

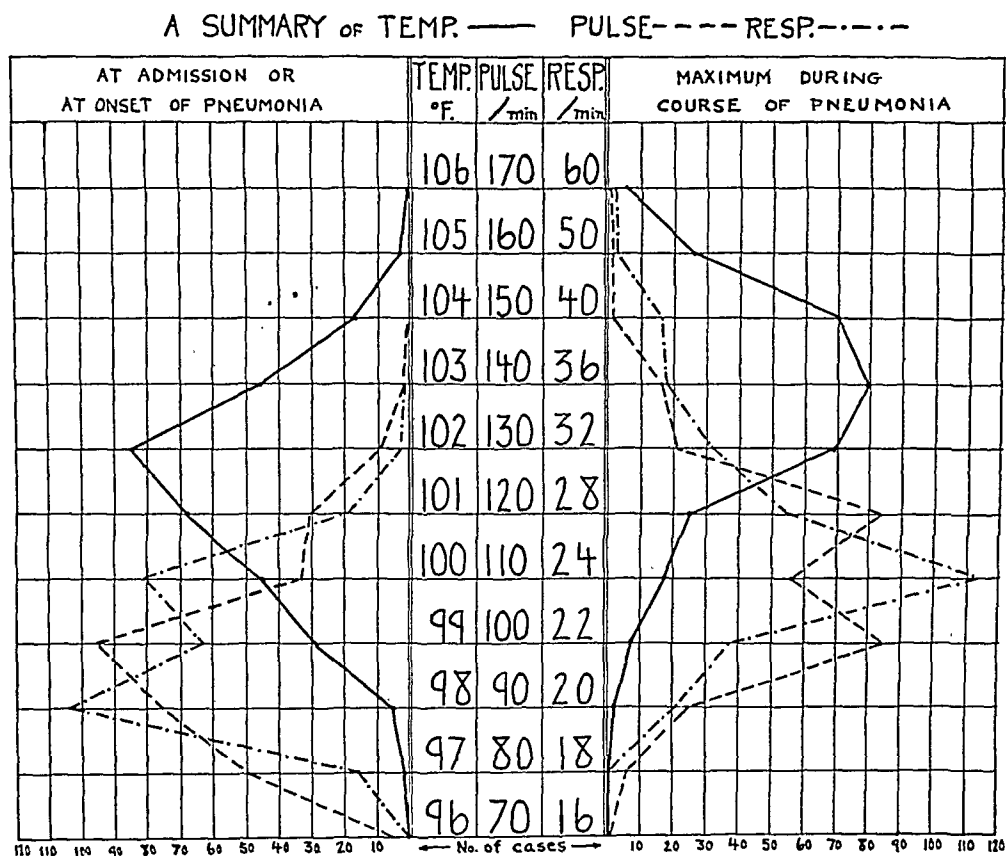
CHIEF COMPLAINT at admission or onset:	No. Cases	ALL SYMPTOMS at admission or onset:	No. Cases
Cough	94	Cough	245
General muscular aching	41	General muscular aching	183
Headache	36	Headache	166
Coryza	33	Feverishness	163
Chest pain	22	Chilliness; chills	151
Feverishness	19	Chest pain	114
Sore throat	19	Sore throat	95
Chills	16	Coryza	94
Weakness	4	Nausea and/or vomiting	34
Congestion in chest	4	Shortness of breath	16
Shortness of breath	3	Spitting of blood	11
Nausea and/or vomiting	3	Weakness	7
Spitting of blood	1	Congestion in chest	5
Pain in abdomen	1	Hoarseness	5
"Hives"	1	Diarrhea	3
Hoarseness	1	Dizziness	2
Diarrhea	1	Pain in abdomen	2
Sore foot	1	Miscellaneous, unrelated	11
Total	300		

universal admission symptom. Few cases experienced hemoptysis; hardly any had dyspnea, whereas over one-third had pain or discomfort in the chest. The largest single group comprised those who reported aches and pains usually occurring in connection with la grippe. (In view of the controversy concerning what should be labelled "influenza," we have tried to avoid loose use of this term, and in none of our cases was virus isolation attempted.) Next to cough, the predominant symptom, then, was that embracing some form of aching—muscular, frontal cephalic, ocular or substernal. A few cases began with conspicuously gastrointestinal rather than respiratory symptoms. Coryza and sore throat were complained of with about equal frequency, approximately one-third of the patients reporting them.

Upon physical examination, as already pointed out, something better than one in two patients showed findings suggestive of pulmonary consolidation. The commonly encountered findings included hyperemia of the nasal and pharyngeal mucosa, hypersecretion of mucus, and the presence of a purulent or mucopurulent secretion if the case had progressed that far. The eyes were often injected, the eyeballs tender to pressure. Slight cyanosis was common, with a flushed face, while marked cyanosis was infrequent. Perspiration tended to be profuse. The respirations were rarely much embarrassed. The patient impressed the examiner as being markedly uncomfortable, but not often as alarmingly ill.

Chest findings ranged from nothing significant at preliminary examination, through the group with well developed tracheobronchitis, up to those where a larger or more accessibly placed patch of consolidation was suggested, first by diminution of intensity of the normal breath sounds over an area, and later by the appearance of the classical signs of greater or less con-

solidated portion of lung tissue. Râles, vesicular in type, often were not distinguishable at first examination, or perhaps only after cough. Sometimes the fine type of r le was not heard at any time, and moist sounds were ascertained only as bubbling r les after resolution was under way. Coarse r les often took many days to disappear. Sputum, too, was very often lacking or extremely scanty during the larger part of the illness, and could be collected only when the pneumonic process was breaking up. Usually it was thick and mucopurulent, seldom rusty or frankly bloody.



Consulting the right-hand portion of figure 2, we see that later in the illness the temperature, pulse and respiration readings usually climbed somewhat higher, though unusually high levels were rare. The pulse was not accelerated in proportion to the febrile response as a rule. This was not merely a common finding, but also a good prognostic indication. Most of the fevers at maximum lay between 102° and 104° F.; the relatively slow pulse rates centered at 110; and the respirations clustered between 22 and 28 per minute.

Four cases were completely afebrile during their stay in the Infirmary. Of the remaining cases, excluding the fatalities, 261, or 87 per cent, showed a return to normal temperatures by lysis, only 24 cases losing their fever by a definite, typical crisis.

Of the febrile cases, we have omitted from consideration those terminating fatally and seven others running a subsequent septic course due to some concurrent infectious process. We found 55 per cent of the remainder had normal temperatures by the sixth day, 72 per cent by the eighth, and 93 per cent by the twelfth day in hospital. A few cases, mostly because of some persistent complication or because of a delayed resolution, remained febrile until from 13 to 26 days had elapsed.

Though it had proved difficult to demonstrate pulmonary consolidation early by physical examination in many instances, in practically all cases it was possible at a later date to determine easily and accurately the presence of a resolving process by this approach. Eight cases showed resolution phenomena upon admission, while by the sixth day 60 per cent of the recovering cases were in that state. By the eighth day 79 per cent showed resorption taking place, by the twelfth day 88 per cent. A straggling six cases took from 13 to 20 days to display resolving signs: three others were obscured by overlying fluid in the pleural cavity; one clinical picture was so confused as to make onset of resolution open to debate; and in 11 instances death supervened before the consolidation had started to dwindle. Comparison of these figures for the sixth and eighth hospital days with those for the febrile status at identical periods reveals that discovery of physical signs pointing to improvement usually antedated by a few days the full resumption of normal figures on the nurse's chart. After the tenth day, however, fever might be absent while a slowed resolution was only becoming evident to chest examination.

ROENTGEN-RAY FINDINGS

All our cases were thoroughly checked by roentgenograms. Films totalling 993 were made upon the 300 patients. These included 779 bedside studies made with a reliable portable machine at a 30- to 36-inch distance, and 214 films, most of them 72-inch stereoscopic plates, made later, on convalescent patients, in the Wisconsin General Hospital roentgenogram rooms. In some instances patients were fluoroscoped.

Exact comparison of ordinary physical examination results with the diagnoses made on a roentgen-ray basis is neither possible nor quite fair so long

as we are unable to report, as controls, how many other Infirmary patients during the eight-year period were suspected of pneumonia, roentgen-rayed, and found to be free of consolidation during the entire course of their illnesses. However, our results are striking enough to serve as indisputable indicators that the film reveals a much higher percentage than does the stethoscope or other routine procedure based on changes in pulmonary and thoracic vibratory phenomena. One is struck by the similarity between the relative merits of roentgenographic and stethoscopic examination in these early pneumonia cases and in patients with early pulmonary tuberculous lesions.

Preliminary physical examination, as stated above, led to a tentative diagnosis of pneumonia in 55 per cent of our cases (table 4). Roentgen-ray studies confirmed this promptly in all but a very few instances where the first film failed to reveal a small or unusually situated patch and only repeated or extraordinary roentgenograms caught the shadow. On the other hand, in the considerable Group II, where pneumonia was developing or was already well established but at so deep a site as to give insufficient physical signs to lead to a diagnosis, roentgen-ray examination was employed because the appearance of the patient, the history, the subsequent course, or the presence of pneumonia in the community made the examiner particularly sensitive to its possibility. In these cases, the vast majority showed a pneumonic involvement as revealed by the very first film obtained. In a few cases, where standard antero-posterior technic failed to disclose pulmonary consolidation, an oblique or a lateral view succeeded in doing so. In this regard, it should be stated that very often pneumonic consolidations in the region of the cardiac shadow are missed on casual scrutiny of antero-posterior exposures. A greater degree of patience, appreciation of anatomical and physical laws, and care in "unscrambling" the relative and frequently overlying densities in such areas will generally suffice to betray the presence of any unusual process disturbing normal lung aeration, and lateral roentgenograms may be then used as a means of corroborating the fact.

Briefly, roentgen-ray diagnosis of pneumonia of the types described represented our sheet anchor, whereas physical examination of orthodox limitations, no matter how careful, unhurried and competent, or how numerous were the examiners, was apt to prove less than adequate. If these observations are supported by the experiences of other clinicians, it becomes mandatory that all severely ill respiratory cases deserve roentgen-ray examination of the chest. We should be appalled, according to old standards, if a thorough chest examination were omitted. Yet we are learning, by present standards, that a really thorough examination of the chest must include a roentgen-ray examination. The drawbacks of expense and lack of proper facilities in many communities seem to be all that stand in the way of chest films being as mandatory as are less revealing but commoner laboratory procedures.

Anatomically, we have divided our cases into two groups, perhaps some-

what arbitrarily—those with involvement of a whole single lobe or less (244 cases), and those showing involvement of two or more lobes or parts of several lobes (56 cases). In this latter category there was involvement of two lobes in 42 instances, of three lobes in five, of four lobes in one, and of all five lobes in one case. Figure 3 pictures the frequency of involvement by lobes, indicating, as reported by other observers, that basal distribution of this variety of pneumonia is the most common. In our 244 cases with single lobe pneumonia, basal lesions outnumbered the others seven to one, while in those multiple lobe cases stemming from single lobe pneumonia primarily,

FREQUENCY OF INVOLVEMENT BY LOBES:

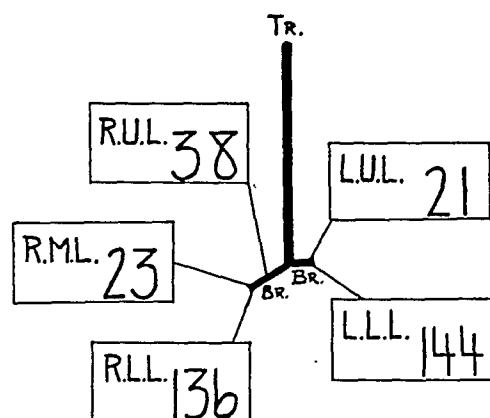


FIG. 3.

the usual experience was to find the initial consolidation in a lower lobe. The left or right lung was about equally often attacked in the single lobe cases, while multiple lobe cases seemed to demonstrate a predilection toward the more numerous lobes of the right side.

In appearance the typical pneumonic consolidation we observed first showed up on the roentgen-ray film as an ill-defined patch or zone of haziness, dependent for its density in large part on the stage in which we first examined and filmed the chest. Successive pictures would show usually a gradual, sometimes a more rapid, increase in the size and heaviness of the shadow if the disease were advancing, with a steady clearing of the area in surviving cases once resolution had begun. In most instances practically no evidence to suggest or locate recent pneumonia persisted, even in the most satisfactory films, four weeks after the onset of the illness. Often all traces had disappeared in three weeks. Last to go was the increase in the adjacent peribronchial markings, or occasionally a slight pleural thickening.

CLINICAL LABORATORY DATA

Our series of cases began at a time when the number of pneumococcal types ended with the old miscellaneous Type IV. Thus, well over half the sputum-producing cases had the benefit of none of the more detailed sputum typing studies to which cases later in the series were subjected. This should be recalled when examining table 6. Even so, it is safe to say that seldom

TABLE VI
Results of Sputum Examinations
(Sputum samples were obtainable in 235 of the 300 cases treated)

A. Division of sputa:		No. Cases
I. Sputa revealed recognizable organisms		131
II. " " no " "		104
Total		235
B. Organisms reported identified:		
a. Streptococci, undifferentiated		56
b. Pneumococci		50
Type I	3 cases	
" II	1 case	
" III	3 cases	
Types IV to XXIX	21 "	
Type IV (old)	18 "	
Not determined	4 "	
c. <i>H. influenzae</i>		2
d. <i>K. pneumoniae</i>		1
e. "Gram-positive Diplococci"		4
" " " Cocci"		2
" " " Bacilli"		1
" " -negative Bacilli"		3
f. Mixed Group		12
Streptococci and Pneumococci	8 cases	
" " <i>H. influenzae</i>	1 case	
" " Gram-pos. Bac.	1 "	
" " " Diplococ.	1 "	
<i>H. influenzae</i> and Pneumococci	1 "	
Total		131

did this early restriction interfere with a reasonably satisfactory sputum analysis in cases such as we are reporting, due to two considerations. First was the relative infrequency of pneumococcal pneumonia. Second was the paucity of sputum in the vast majority of cases during the early days of their illness. What did appear was the preponderance of streptococci in the sputa that were obtainable.

In the 300 cases, we were able to secure one or more sputum samples in 265 instances. From 104 of these latter, the specimens revealed no recognizable organisms. Table 6 summarizes the results of laboratory studies on the remaining sputa of 131 individuals. It will be noted that streptococci, either alone or with other organisms, occurred oftener than any other bac-

terial form identified. Next in order came the pneumococci. Only in four cases were reports received that *H. influenzae* had been found. Virus studies of nasopharyngeal washings, etc., as recommended by Reimann,⁹ were not attempted in our series.

We did not consider sputum examinations satisfying or complete unless a determined search had been conducted to rule out the possibility of tubercle bacilli as the etiologic agent. Of the 235 cases giving sputum, 229 supplied a total of 777 sputum samples, ranging from 1 to 11 per patient, and collected during the resolving stage of their pneumonia. In no case were acid-fast bacilli observed to be present, several cases being additionally

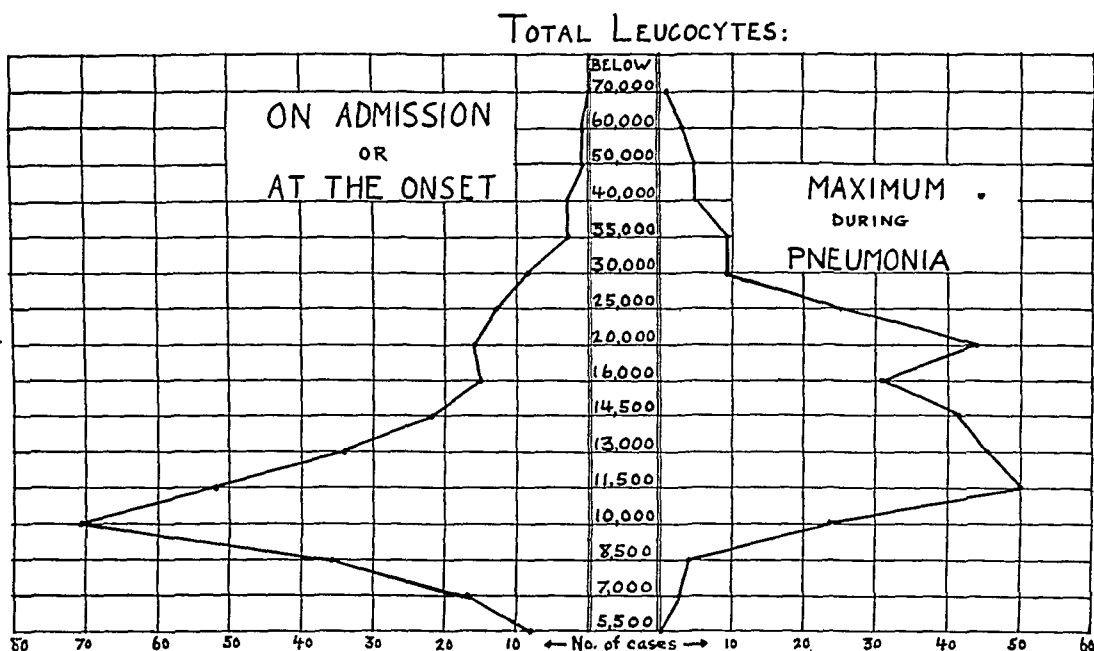


FIG. 4.

checked by examination of fasting gastric contents. During the eight-year span of 368 pneumonias, however, two cases of proved tuberculous bronchopneumonia did occur. They were both omitted from the present statistics and report.

Red blood cell counts were not made on every case, but were done at intervals in the greater number, generally during convalescence. A moderate degree of secondary anemia often developed, responding rapidly to appropriate corrective therapy. We did not observe any severe anemias in our uncomplicated pneumonias.

Blood cultures were seldom deemed necessary, though they were carried out in approximately 30 cases. Bacteremia was proved in one Type II and one Type III pneumonia, and in two fatal cases hemolytic streptococci were isolated.

Throat cultures were obtained in about 30 cases, usually those showing some degree of follicular tonsillar or pharyngeal involvement. Whenever the organisms were identifiable, they proved to be streptococci of strains similar to those found in the sputa.

Routine urinalyses, frequently run, gave us no consistent abnormal trends. A few cases displayed a transient albuminuria of mild nature, with occasional flurries of white blood cells, rarely a few erythrocytes. On two occasions we encountered a mild, acute, non-specific cystitis, and once an acute toxic nephritis that cleared soon.

DIFFERENTIAL WHITE BLOOD CELL COUNTS
AT
HEIGHT OF PNEUMONIAS

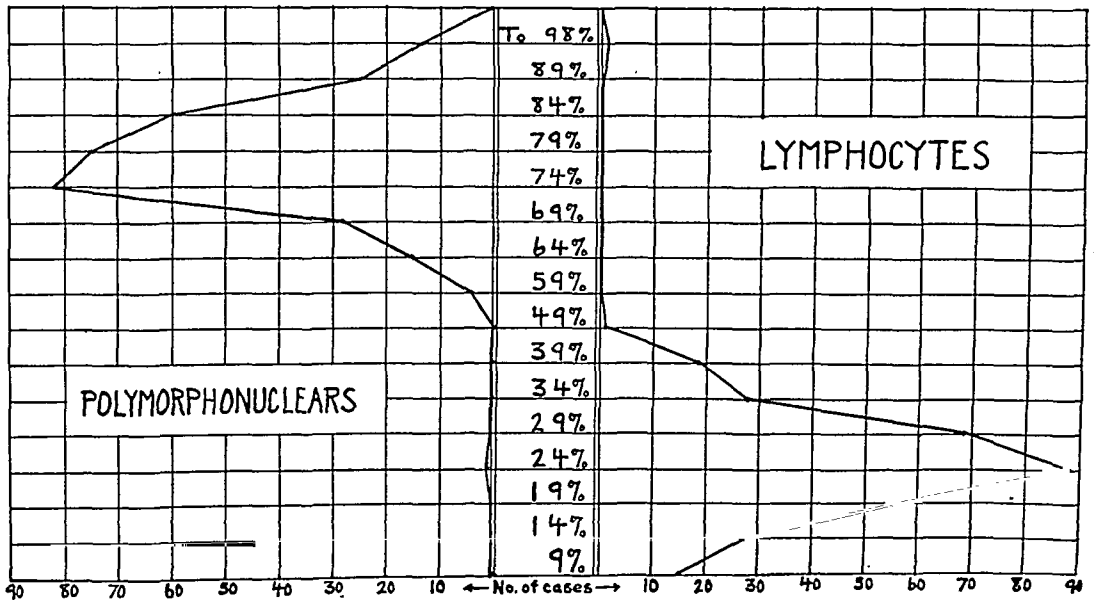


FIG. 5.

Total leukocyte and differential leukocyte counts were made upon admission to hospital and repeated at very frequent intervals during the illness and through the early portion of convalescence. In figure 4 we have shown, on the left, that the admission white blood cell count did not tend to be greatly increased, but favored the zone from 8,500 to 13,000, with more cases showing 10,000 leukocytes on entering the Infirmary than any other total. The right-hand side of the same chart reveals the expected heightened leukocytosis during the patients' most critical days of their pneumonia. Even then, however, the maximum counts were not, as a rule, very high when compared with severe lobar pneumonia determinations, grouping themselves largely in the 10,000 to 25,000 bracket. Murray⁸ has drawn attention to "a curious rise in the count during convalescence, occasionally reaching 17,-

000 to 20,000." He goes on to remark that: "While this might be taken to herald the onset of some complication, none appeared in this group." Since he offers no theory to explain the phenomenon, perhaps we should say that we have observed this secondary rise in leukocytes in cases of pneumonia for many years, and, indeed, it was present in the greater share of the cases here reported. In our experience, barring the very occasional case in which it may indicate a late spread of the pneumonia or the occurrence of some complication, this secondary leukocyte peak has always accompanied the establishment and prosecution of the resolution process. We regard it as a very favorable sign, and have yet to witness our optimism as misplaced.

Figure 5 summarizes the differential white blood cell proportions of a typical specimen count at the time the pneumonic invasion was at its height and the patient at his sickest. Again, unlike the findings in cases of so-called typical pneumococcus pneumonia, the response in our patients was moderate rather than sweeping. The greatest number of cases had a count that read approximately: Polymorphonuclears, 70 to 85 per cent; lymphocytes, small and large, 30 to 15 per cent. The chart shows that peaks jut out at about 74 per cent and 24 per cent respectively, the missing 2 per cent accounted for by rarer types of cells. Here again our figures are extremely close to agreement with those reported by others for this variety of pneumonia among young adults.

COURSE AND PROGNOSIS

As stated before, there were 11 fatalities among 300 cases, nine of them due primarily to pneumonia. We can further break down our series into 234 cases in which no obvious complications occurred, 55 marked by one or more complicating factors, nine pneumonia deaths, one death due to subacute bacterial endocarditis, and one due to purulent pericarditis.

In the uncomplicated group, the average stay in the Infirmary was 18.8 days, 42.9 days for the cases suffering complications, and 8.2 days for those succumbing to pneumonia. These last cases died two to three days after the stage at which most other cases demonstrated that satisfactory resolution was under way. Lane ⁴ has reported a series in which, in bronchopneumonia of fatal termination, 41 per cent of the illnesses extended beyond one week. With regard to the number of hospital days for the uncomplicated cases, it should, of course, be remembered that these were students forced to face a rented room or a dormitory or a trip home in inclement weather following their discharge from bed care. Accordingly, we were most conservative in making certain that they stayed long enough to make their leaving reasonably safe.

The commonest complications in order of their frequency are listed in table 7. Pleural involvement, simple effusion, dry, or with empyema formation is seen to lead the roster, as also reported by Schwartz ¹⁰ and by

Kohn and Weiner.³ Acute middle ear infection is in second place. Fatal issue is listed third.

TABLE VII
Complications Most Commonly Encountered

		No. Cases
Pleurisy		24
With simple effusion	15	
Dry	5	
With empyema	4	
Acute otitis media		14
Fatal issue		11
Acute paranasal sinusitis		7
Atelectasis; massive collapse		7
Acute follicular tonsillitis		4
Acute eustachian pyosalpingitis		4
Acute toxic myocarditis		3
Spontaneous pneumothorax		3
Markedly delayed resolution		3
Acute pericarditis		2
Acute nonspecific cystitis		2
Acute nephritis		2
Infectious mononucleosis		2

Deaths occurred in every one of the eight years except 1933-1934. The year 1937-1938 was marked by three pneumonia fatalities. Paradoxically, the greatest occurrence of complications in comparison with the number of pneumonia cases treated was in 1931-1932, the year when least pneumonia was seen on the campus. In that year there actually were more complicated than uncomplicated cases, and in two of the 15 cases death resulted. This bears out the observation of Bullowa and Wilcox¹ and others that mortality rates vary from year to year, along with the incidence of various types of organisms of fluctuating virulence.

TREATMENT

The therapy was very largely symptomatic and supportive. Serum was only occasionally used, partly because it was not often indicated, partly because of the lateness of recovery of sputum containing any demonstrable organisms, let alone type-positive pneumococci susceptible of serum treatment. In all, four cases received anti-pneumococcus serum, with questionable benefit in one case. Sulfanilamide was used in a small number of cases late in the series again with lack of more than occasional or supplemental benefit. Certainly, there were no dramatic recoveries attributable to the use of drugs in the sulfonamide group. This observation has since been corroborated by the experience of one of us at another college in dealing with cases of student pneumonia during the past five winters.

Codeine for cough, morphine for pain, restlessness and fright were decidedly helpful. Forcing of fluids was a routine procedure except when rarely or temporarily contraindicated. In our opinion, mustard as a counter-

irritant was appreciated both by the patient and the doctor, relieving pain and chest tightness in most instances. We employed hot packs or warm turpentine stupes to the abdomen in the occasional cases where abdominal distention was a problem. Enemata were useful, but were of the mild soda-saline variety, often preceded by an oil retention enema overnight, and always reserved as an emergency procedure so as not to exhaust a patient already fully occupied in battling a treacherous disease.

Oxygen therapy was not reserved for late or overwhelming emergencies. We employed it liberally to allay such exhausting symptoms as severe cough and dyspnea of neurogenic origin, as well as to combat the infrequent cyanosis and true air-hunger. We found oxygen often relieved otherwise ungovernable headache, especially in those patients not tolerating codeine well. As Jonxis² has emphasized, hypoxemia is not necessarily associated

TABLE VIII

Surgical and Other Procedures Necessary during Pneumonia

	No. Cases
Paracentesis of thorax, diagnostic	15
Transfusion of blood	5
Paracentesis of auditory tympanum	5
Rib resection; thoracic drainage	3
Incision of abscess	2
Antrum puncture	1
Thoracoplasty, 3-stage	1
Mastoidectomy, bilateral	1
Paracentesis of pericardium (4 times)	1
Pericardotomy	1
Appendectomy	1
Extraction abscessed tooth	1
Ligation right jugular vein	1

with marked cyanosis. We administered oxygen by the nasal catheter method, generally under the direction of Waters and his associates. This method was not only well borne by our patients, but was easy, economical and effective in the hands of our staff. In most cases the gas was supplied uninterruptedly at the outset, later only at those times when some symptom or the patient's attitude necessitated its use. In addition to the 11 fatal cases, oxygen was used on 42 other individuals, always with favorable results. In a few cases it proved to be the only therapeutic agent capable of controlling extreme paroxysms of cough. Oxygen was employed during part or all of 333 separate days, averaging 6.3 days per case receiving it. We consider oxygen, after the fundamentally necessary bed rest, as our greatest single ally and comfort-providing agent in treating the type of pneumonia under discussion.

Seldom were surgical procedures necessary, though when need did arise they ranged all the way from a diagnostic pleural paracentesis up to rib resection or jugular ligation. These interventions are listed in table 8.

SUMMARY

1. Reported are 300 consecutive cases out of a total 368 cases of pneumonia occurring among students at the University of Wisconsin, Madison, during eight academic years beginning July 1, 1931, and ending June 30, 1939. All cases were treated at the Student Infirmary.

2. Relation to other types of respiratory illness is discussed. The kind of pneumonia predominating in this series seems more closely linked to acute respiratory tract infections than to any other type of illness.

3. The symptomatology, physical findings, course, complications, prognosis and treatment are summarized. Specific therapy was not generally practiced. The value of oxygen therapy is stressed.

4. Roentgenographic and clinical laboratory data are presented and typical findings discussed.

5. A mortality rate of 3.6 per cent is reported.

CONCLUSIONS

1. Pneumonia occurs frequently in a mass of young adults such as a university student body, among whom acute respiratory infections are the chief cause of morbidity.

2. Pneumonia in such a group carries a low mortality due to the high general health level in the ages and the social stratum concerned, the fairly low virulence of the average infective agent encountered, and the prompt and effective diagnostic and therapeutic services available. Such factors should be envisaged when results of serotherapy, chemotherapy or other treatment involving young adult pneumonia cases are reported.

3. Though the mortality rate is low for pneumonia, 3.6 per cent, this disease accounts for more fatalities on the campus than any other cause of death.

4. Streptococci lead as the causal organisms found, followed by pneumococci usually of low virulence.

5. Roentgen-ray examination greatly excels less penetrating methods of pulmonary examination.

6. The form of pneumonia described can be considered common among the group observed, and compares closely with similar studies reported by recent and contemporary observers of related groups. Therefore, it seems unnecessary and unwise to label this as an "atypical" pneumonia, or to coin terminology that suggests a process not covered by the thoroughly adequate word pneumonia.

REFERENCES

1. BULLOWA, J. G. M., and WILCOX, C.: Pneumococci types and their variations in incidence and mortality for adults and children, *Arch. Int. Med.*, 1937, lix, 394-407.
2. JONXIS, J. H. P.: Arterial oxygen saturation and effect of oxygen therapy in pulmonary diseases, *Am. Jr. Dis. Child.*, 1939, lvii, 58-67.

3. KOHN, J. L., and WEINER, S. B.: Pneumonia in children. A survey of 1000 cases with attempted follow-up, *Am. Jr. Dis. Child.*, 1936, li, 1095-1100.
4. LANE, F. A.: Pneumonia in the Westchester County (N. Y.) Health District, 1931-35, *New York State Jr. Med.*, 1939, xxxix, 225-231.
5. LOCKE, A.: Lack of fitness as the predisposing factor in infections of the type encountered in pneumonia and in common cold, *Jr. Infect. Dis.*, 1937, lx, 106-112.
6. MCKINLAY, C. A., et al.: Acute respiratory tract infections including pneumonia in a young adult group, *Proc. Staff Meet. Univ. Minn. Hosp.*, 1940.
7. MILLER, F. N., and HAYES, M. G.: Bronchopneumonia of mild severity at the University of Oregon, *Northwest Med.*, 1939, xxxviii, 12-14.
8. MURRAY, M. E., JR.: Atypical bronchopneumonia of unknown etiology, *New Eng. Jr. Med.*, 1940, ccxxii, 565-573.
9. REIMANN, H. A.: An acute infection of the respiratory tract with atypical pneumonia, *Jr. Am. Med. Assoc.*, 1938, cxi, 2377-2384.
10. SCHWARTZ, J.: Pneumonia: a review of cases at the Beth-El Hospital for the ten years, 1927-1936, *Med. Rec.*, 1938, cxlvii, 195-200.
11. SMILEY, D. F., et al.: Acute interstitial pneumonitis, *Jr. Am. Med. Assoc.*, 1939, cxii, 1901-1904.
12. SMITH, F. H.: Pneumonia over a period of twenty-five years, *Va. Med. Month.*, 1937, lxiii, 735-739.

HEMORRHAGIC PLEURAL EFFUSION; AN ANALYSIS OF 120 CASES *

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FEW papers have been written on the subject of hemorrhagic pleural effusion during the past 10 years. There are discussions of the subject which are part of an exposition of single underlying diseases.¹ There are other discussions of hemorrhagic pleural effusion which limit themselves to its occurrence in children.^{2, 3} But there is no comprehensive study of the entire subject except chapters in textbooks on diseases of the chest^{4, 5} which, however, fail to give the sources for their conclusions. Views expressed in the older literature^{6, 7} are now open to question in the light of our better knowledge of various diseases, particularly carcinoma of the lung.

For these reasons, it was decided to make a statistical investigation of hemorrhagic pleural effusion to determine the relative frequency of the underlying diseases. The present paper reports the results of this investigation. It is based on the varied case material of a large general hospital. The series reported here includes the more common types of hemorrhagic pleural effusion, and it also includes a number of cases of unusual etiology which seemed of sufficient interest to warrant detailed discussion.

The clinical records of all patients treated for diseases of the pleura on the wards of the Mount Sinai Hospital during the 11 year period 1928 to 1938 were examined, and 120 cases of hemorrhagic pleural effusion were found. An autopsy was performed on 33 of the patients. In each of the 120 cases, the evidence for the diagnosis of the underlying disease was critically analyzed. Note was also made of the amount and character of the pleural fluid. Where cytological and bacteriological examinations of the effusion had been made, their results were also recorded.

A pleural effusion may be called hemorrhagic if it contains an admixture of blood large enough to be seen macroscopically. It is by no means unusual to find microscopic amounts of blood in a serous pleural effusion of simple inflammatory origin; but the number of red blood cells is too small to cause a change in the color of the effusion. Dieulafoy⁷ found that the presence of 1000 to 3000 red cells per cubic millimeter caused no appreciable change in the color of the fluid, but that 5000 to 6000 red cells per cubic millimeter imparted a rosy tint to the fluid. My observations confirmed Dieulafoy's statement. In 18 cases, a red cell count of the fluid was done. In most of these, the number of erythrocytes far exceeded 6000 per cubic millimeter. In three cases, however, there were fewer, 1500, 2000, and 3080 respectively, and yet the fluid was described as slightly serosanguinous. The color of

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the fluid was usually brownish or amber—produced, no doubt, by changed hemoglobin from laked cells. A rosy tint was more often found as the result of needle puncture, where fresh blood was admixed.

On the other hand, if pure blood, not a serosanguinous fluid, fills the pleural cavity, we no longer speak of a hemorrhagic pleural effusion, but of a hemothorax. In the present study, there were only seven cases in which "pure blood," "old clotted blood," or "chocolate colored material" was aspirated from the pleural cavity. In all the remaining 113 cases, a true effusion was found; this was serous, with a varying admixture of blood leading to such descriptions as "blood-tinged" or "serosanguinous." All traumatic cases of hemothorax, such as those resulting from stab wounds or other chest injuries, were excluded from this series.

Spontaneous Hemopneumothorax. Six cases of spontaneous hemopneumothorax * seen on the wards during 1928 to 1938 were likewise excluded from the statistical analysis, but will now be briefly discussed. In one of the six, inoculation of a guinea-pig showed tuberculosis to be the underlying disease. This patient recovered. The remaining five were of the so-called idiopathic type, and were presumably due to rupture of subpleural blebs. Four of these five patients recovered; one died, and necropsy revealed numerous subpleural blebs. A characteristic finding in all six cases was the hemoglobin content of the aspirated fluid which was high compared to that found in hemorrhagic effusions. In one instance, it was as high as 80 per cent at the outset, but gradually dropped to 5 per cent. The only conceivable explanation for the drop is that the bulk of the blood in the pleural cavity coagulated and more and more red cells were caught in fibrin. Slow clotting of the aspirated fluid was another significant observation made in these cases. It is explained by the transformation of available fibrinogen into fibrin within the pleural cavity. The differential white cell count of the aspirated fluid was done in two of the six cases. In one, it showed 70 per cent polymorphonuclears and 30 per cent lymphocytes, which was practically identical with the differential count of the patient's blood. In the other case, the count revealed 16 per cent polymorphonuclears.

After a spontaneous hemopneumothorax has existed for some time, and frank bleeding has ceased, the character of the pleural contents is apt to change. The clotted blood may act as an irritant on the pleura and may lead to exudation of serous fluid and lymphocytes. This exudate may dilute the blood and eventually the pleural contents may appear to be serosanguinous. At that stage, it may no longer be possible to make the distinction between hemorrhagic pleural effusion and hemopneumothorax.

Bleeding as a Result of Needle-Puncture. Special care was taken to eliminate those cases in which the bloody admixture appeared to be the result

* In one of these, the presence of air could not be demonstrated. Since the paper was submitted for publication, this patient has developed signs of rheumatic heart disease, pericardial effusion, and bilateral pleural effusion. The correctness of the original diagnosis, therefore, may be questioned.

of trauma, during aspiration of the chest. The bloody character of the effusion, in the great majority of cases, was unquestionably not the result of such trauma. In numerous instances,* one or more repetitions of the thoracocentesis proved this by yielding the same type of exudate each time.

Cases where the aspirating needle had punctured a vessel were usually easy to recognize. In such instances, only the first few cubic centimeters of the exudate appeared bloody, the large remainder was serous; or aspiration first yielded a large quantity of clear, yellow exudate, and toward the end of the procedure, fresh blood suddenly appeared, usually after the needle had been manipulated. The probability of puncture of the lung is great when the effusion is very small, so that no significance should be attached to the finding of blood, when only a few cubic centimeters are aspirated. Therefore, cases in which only small amounts of bloody fluid could be obtained on aspiration, were excluded from this series.

EFFUSIONS DUE TO MALIGNANT NEOPLASMS

Neoplasms of the pleura were found to be the most frequent cause of hemorrhagic pleural effusion. Seventy-eight of the 120 patients suffered from malignant neoplasms (65 per cent). To that extent my figures confirm the opinion commonly held that the finding of a hemorrhagic effusion is strongly suggestive of neoplastic disease. Forty-two of the 120 cases, however, were found to be due to other diseases. In other words, every third case was *not* due to neoplasm. It is necessary to bear this in mind when dealing with a case of hemorrhagic pleural effusion. To assume at once that such an effusion is caused by a neoplasm, is a serious error.

The evidence for the diagnosis of malignant neoplasm was carefully analyzed in each case. This diagnosis was proved by postmortem examination in 19 cases, by biopsy in 28 cases, and by the finding of tumor cells in the pleural fluid in 17 cases. In 13 cases, indirect evidence for the diagnosis was accepted, namely characteristic clinical or roentgen features in conjunction with fatal issue in nine cases, and definite physical or roentgen-ray signs of other metastases without proof of fatal issue, in four cases. One case was included although there was no definite proof of the existence of metas-

* Fifty-three out of 78 cases of hemorrhagic pleural effusion due to neoplasm had more than one aspiration. In 10 of these, the fluid obtained was serous at the first aspiration, and serosanguinous later. These were cases in which the possibility of bleeding due to needle puncture had to be considered. In the remaining 43 cases, the fluid was serosanguinous from the first aspiration. In 39 of these 43, the character of the pleural fluid was the same on subsequent aspirations as on the original one. In 4 cases, there was a change; serosanguinous fluid was found at the first thoracocentesis, serous fluid at a subsequent one, and again serosanguinous fluid at a still later one. In these four cases, the bloody admixture to the pleural fluid was certainly not due to needle puncture. Such changes in the appearance of the fluid may rather be explained as a result of repeated hemorrhage into the pleura, an event which is occasionally seen in the course of a pleural neoplasm. Not once did we see a case where serosanguinous fluid was obtained at the first aspiration, but clear serous fluid at all subsequent aspirations. This fact also seems a good argument against the assumption that the blood in some of the pleural effusions which were tapped only once, might have been due to needle puncture.

tases and no knowledge of fatal issue, because other clinical features were definitely indicative of neoplasm.

Primary Pleural Neoplasms. In only one of the 78 cases was the tumor a primary neoplasm of the pleura. This was a case of mesothelioma of the pleura, proved by postmortem examination. It was accompanied by a recurring massive serosanguinous effusion. The fluid had a specific gravity of 1.015 and contained only 900 white blood cells per cu. mm., 96 per cent of which were lymphocytes.

TABLE I
Underlying Condition of Hemorrhagic Pleural Effusion—120 Cases

Malignant neoplasms	Tuberculosis				Miscellaneous inflammatory conditions				Pulmonary embolization	Pelvic fibromatous tumors	Lymphatic leukemia	Lymphogranulomatosis	Uremia associated with cardiac failure	Cause undetermined
	"Idiopathic" effusions	Chronic pulmonary tuberculosis	Polyserositis	Laennec's cirrhosis	Sepsis	Lobar pneumonia	Bronchopneumonia in luetics	Bronchopneumonia in non-luetics						
	4	1	2	1	4	2	2	2						
								Lung abscess						
								Polyserositis						
78	8				13				10	2	2	1	1	5

Metastatic Pleural Neoplasms. The remaining 77 cases of malignant disease were found to be due to metastatic neoplasms of the pleura (table 2). Fifty-one of these 77 cases were histologically proved to be carcinoma, 10 were different types of sarcoma.* In 16 cases, the exact type of tumor was not histologically determined.

In each case, an attempt was made to find the location of the primary neoplasm which had metastasized or extended into the pleura. The primary

* Four of these were lymphosarcomata, and one a myelosarcoma.

TABLE II
Types of Neoplasm Underlying Hemorrhagic Pleural Effusion in 78 Cases

	Primary Pleural Neoplasm	Metastatic Pleural Neoplasms						
	Meso- thelioma	Carcinoma	Neoplasm of unde- termined type	Sarcoma	Lympho- sarcoma	Angio- sarcoma	Fibromyo- sarcoma	Rehal neoplasm
No. of Cases	1	50	15	4	4	1	1	2

lesion was found in the lung more often than in any other organ. Thirty-one of the 77 metastatic cases were proved to be due to primary neoplasms of the lung. In eight additional cases, it was not possible to determine the site of the primary tumor with certainty, but an analysis of the clinical and roentgenological features made it appear very probable that the primary lesion was in the lung. In any event, no more than 39 of the 77 cases, i.e. half, were cases of primary pulmonary neoplasm. It is noteworthy that in none of these 39 cases was the effusion bilateral.

In the other half of the cases, the primary tumor was situated in various other organs (table 3). In 10 patients, the site of the primary tumor could

TABLE III
Site of the Primary Tumor in 78 Cases of Hemorrhagic Pleural Effusion Due to Malignant Neoplasm

	Pleura	Lung	Probably in lung	Breast	Mediastinum	Colon	Kidney	Tonsil	Other viscera	Unknown—probably in viscera other than lung
No. of Cases	1	31	8	8	13	2	2	1	2	10

not be determined, but it was probably situated in viscera other than the lungs. A conclusion of practical importance may be drawn from these figures: in every case of unilateral hemorrhagic effusion which is suspected of being of neoplastic origin, it is appropriate to begin the diagnostic studies with an investigation of the lung.

Size of Effusions Due to Neoplasm. Pleural effusions due to neoplasm, as is well known, are often of very large size, covering the lung from apex to base and failing to show evidence of absorption. In our series, 60 of the

78 cases of neoplasm had such large effusions, each yielding more than 1000 c.c. on aspiration; several were of huge size, requiring many aspirations and yielding 10,000 c.c. and more of fluid. Only nine effusions were of small size, less than 500 c.c. being obtained by thoracocentesis in each of them. The effusion was bilateral in eight, right-sided in 34, left-sided in 36 cases.

Character of Fluid. In 71 of the cases of neoplasm the aspirated fluid was serosanguinous; in seven cases, however, it was described as "pure blood," "thick blood," "old, clotted dark blood," "dark brown old blood." In one of these seven cases, the fluid changed in character. At first, pure blood was obtained in large quantities on several aspirations; a few weeks later the fluid became serosanguinous. Frank hemorrhage into the pleura from a tumor is not a very unusual occurrence. On the other hand, in the non-malignant cases, pure blood was never found in the pleural cavity, except in cases of spontaneous hemopneumothorax.* It seems justifiable to infer that the finding of pure blood in the pleural cavity limits the differential diagnosis to two conditions: spontaneous hemopneumothorax and neoplasm of the pleura.

The specific gravity of the pleural fluid was examined in 43 cases. It was found to range between 1.010 and 1.030, with an average of 1.017. In the large majority (29 cases) it was 1.015 and above. In only three cases it was below 1.012.

Cytological Examination of the Pleural Fluid. This included a red cell count, a white cell count, a differential count of the leukocytes, and a search for tumor cells. In two of the cases where "pure blood" was aspirated, the hemoglobin content of the fluid was also estimated. It was 28 per cent in one, and 35 per cent in the other.

In 34 cases, the leukocytes were counted. The average number was 3200 per cu. mm., but the number varied from 60 to 19,700. In 19 cases, the leukocyte count was 1000 or below. Here again, it should be borne in mind that such cell counts are not always reliable, particularly if the fluid has begun coagulating. In that event, only the supernatant fluid may have been examined, whereas the majority of the cells were caught in the clot.

A differential count of the leukocytes in the fluid was made in 34 of the 78 cases of pleural neoplasm. In the majority of these, the leukocytes were almost all lymphocytes, in spite of the fact that the effusions were hemorrhagic. That lymphocytes usually predominate in cancerous effusions does not seem to be generally known, for Norris and Landis⁴ write: "An excess of lymphocytes in the fluid is very suggestive of tuberculosis." Only 12 of the 34 cases showed more than 15 per cent of polymorphonuclears. It was also apparent that the percentage of polymorphonuclears varied with the amount of blood admixed with the fluid. In the few cases where the pleural contents resembled pure blood, the percentage of polymorphonuclears was very high. In some of these the differential white cell count in the pleural

* With one exception; see the first footnote.

fluid approximated the differential leukocyte count in the patient's blood. Two effusions in which the white cell count was very high, 18,400 and 19,700 respectively, contained a high percentage of polymorphonuclears, 55 per cent and 95 per cent.

Examination for Tumor Cells. In 70 of the 78 cases of neoplasm, the pleural fluid was examined for tumor cells by the paraffin section method of Mandlebaum.⁸ In 35 cases (50 per cent), tumor cells were found. In 17 of these, the finding of tumor cells was the only available proof for the diagnosis of neoplasm. If primary mediastinal neoplasms are omitted, the percentage of cases in which tumor cells were found becomes higher, namely 55 per cent. In 25 of the 35 positive cases, tumor cells were found at the first examination, in five at the second, in three at the third, and in two at the fourth. In 35 of 70 cases examined, tumor cells could *not* be found in the pleural fluid, the diagnosis being established by other means. Nearly half of these failures, 17, occurred in patients who had only a single examination of the fluid. Had they had several more examinations, tumor cells might still have been found in some of them.

TABLE IV
Hemorrhagic Pleural Effusions Due to Malignant Neoplasm; Frequency of Finding of Tumor Cells in Pleural Fluid

Site of primary tumor	Pleura	Lung	Probably in lung	Breast	Mediastinum	Colon	Kidney	Tonsil	Other viscera	Unknown—probably in viscera other than lung	Total number of cases	Cases examined for tumor cells
Number of Cases	1	31	8	8	13	2	2	1	2	10	78	70
Tumor cells found in fluid	0	17	5	6	3	0	0	0	0	4	35	50% positive
Tumor cells not found in fluid	1	13	3	1	8	0	2	0	2	5	35	50% negative
Fluid not examined for tumor cells	0	1	0	1	2	2	0	1	0	1	8	

Table 4 shows that the frequency with which tumor cells were found varied with the location of the primary neoplasm. With the primary tumor situated in the mediastinum, tumor cells were found in only two out of ten cases examined (20 per cent). This low incidence contrasts with the much higher percentage of positive examinations for tumor cells in the neoplasms originating elsewhere. When the primary tumor was in the breast, tumor cells were found in the pleural fluid in six out of seven cases examined. When the primary tumor was in the lung, tumor cells were found in 22 out of 39 cases.

The amount of blood admixed with the pleural fluid did not seem to affect the frequency with which tumor cells were found. Where the aspirated fluid consisted of pure blood, tumor cells were found in the same percentage of cases as where it was serosanguinous.

Tumor Cells in Serous Effusions. Are tumor cells found more frequently in hemorrhagic effusions than in serous ones? To obtain an answer to this question I collected an additional series of 25 cases of *serous* effusion due to proved metastatic carcinoma of the pleura, with the primary tumor situated either in the lung or in other viscera, the mediastinum excepted. Tumor cells were found in 13 of these 25 cases (52 per cent), an incidence not significantly lower than that found in *hemorrhagic* pleural effusion due to malignant neoplasms (55 per cent), mediastinal tumors again excepted. Although this series is small, it appears justifiable to conclude that the presence of blood in the effusion does not indicate the existence of an ulcerative process causing increased desquamation of tumor cells.

EFFUSIONS NOT DUE TO MALIGNANT NEOPLASMS

Table 1 lists the different diseases which were found to cause hemorrhagic pleural effusions. They were malignant neoplasms, miscellaneous inflammatory conditions, tuberculosis, pulmonary embolism, uremia associated with cardiac failure, pelvic fibromatous tumors, Hodgkin's lymphogranulomatosis, and lymphatic leukemia. Table 1 shows, besides, a group of five cases in which it was impossible to determine the nature of the underlying disease. That they were not due to malignant neoplasms was proved for four of the five by their favorable outcome.

In the non-malignant group, the most frequent cause of hemorrhagic pleural effusion was inflammatory disease of the pleura. The recognition of such cases is of great prognostic and therapeutic importance. It is not surprising that an inflammation of the pleura, especially a severe one, should be associated with injury to the capillaries, and therefore, with a hemorrhagic pleural exudate. At least 21 of the 120 cases of this series were due to inflammation of the pleura. Eight occurred in association with pulmonary tuberculosis, and 13 in association with miscellaneous inflammatory conditions. (The five cases in which the underlying disease was not determined, are not included here, but the disease was probably of an inflammatory nature in most of them.)

Tuberculosis. Tuberculosis is well known to be a common cause of serofibrinous effusion. Hemorrhagic effusions of tuberculous etiology, however, appear to be much less frequent. Only eight of the 120 cases of this series were due to tuberculosis.* This low incidence contrasts with the statement made by Norris and Landis,⁴ that tuberculosis is the most common

* Besides these eight, tuberculosis was the underlying disease of one of the cases of spontaneous hemopneumothorax discussed before. Tuberculosis may also have been the cause of one or two of those hemorrhagic pleural effusions, in which it was impossible to determine the underlying disease. (Table 1, last group.)

cause of blood-stained effusions. The low incidence of tuberculosis in our series may in part be due to the relatively small number of tuberculous patients who are granted admission to the Mount Sinai Hospital. It is most probable that statistics derived from institutions for the tuberculous show that a large majority of cases of hemorrhagic pleural effusion are tuberculous (because of the very nature of the cases admitted to these institutions). Our statistics are based on the experience obtained in a general hospital, not in an institution for the tuberculous. It is a known fact that pleural effusions are unusual in well developed cases of clinical pulmonary tuberculosis. On the other hand, it is characteristic of tuberculous pleural effusions that they occur in patients who have no symptoms referable to a pulmonary lesion, patients in whom the sputum is negative and a definite diagnosis of tuberculosis is rarely made before they are admitted to a hospital. It may, therefore, be assumed as probable that the experience with pleural effusions at the Mount Sinai Hospital will parallel that which is encountered in ordinary practice.

In six of the eight cases the tuberculous origin was proved; in five by a positive guinea-pig test, and in one by a positive sputum.

In four of the eight cases, the effusion was the first clinical manifestation of tuberculosis. All four were young people. Clinically, these four cases appeared to belong in the group of so-called "idiopathic" pleural effusions. In all cases of idiopathic *serofibrinous* effusion, most of which are believed to be tuberculous, a few erythrocytes are found in the fluid. It is, therefore, not surprising that occasionally enough red blood cells should be present to stain the exudate. The number of white blood cells per cubic millimeter was small, usually below 1000, and they were mostly lymphocytes (95 per cent, 95 per cent and 96 per cent lymphocytes in three of the four cases in which a differential count was made). Norris and Landis⁴ consider such a high percentage of lymphocytes as very suggestive of tuberculosis. Our observations in cases of carcinoma do not confirm this statement. An equally high percentage of lymphocytes was found in many cases of neoplasm, especially when the amount of blood admixed with the fluid was small.

A definite tuberculous etiology was proved in two of these four cases. One patient whose fluid gave a negative guinea-pig test, developed an exudative pulmonary tuberculosis with positive sputum the following year. The other showed a positive guinea-pig test after injection of the fluid. This patient has remained well and free from any roentgen-ray signs of pulmonary tuberculosis for five years. The third and fourth were cases of pleuritis with a serosanguinous effusion in which the tuberculous etiology was not proved. In the third case, the Mantoux reaction was positive and the fluid lymphocytic. The patient (19 years) was in the age group in which tuberculous pleuritis is most common, and the course of the disease was marked by fever for three weeks, followed by the slow absorption of the fluid; a thickened pleura remained. Although the case was grouped as one of "idiopathic pleurisy," it may be presumed that it really was tuberculous in nature. The fourth patient was a 17 year old negro with an idio-

pathic pleurisy who entered the hospital with a temperature of 104 degrees. He had fever for a period of eight weeks before the temperature subsided to normal. The Pirquet test was positive. On the first aspiration, two weeks after the onset, the fluid was slightly turbid and contained 2000 leukocytes per cu. mm., of which 95 per cent were lymphocytes. There were only 1000 red cells per cu. mm. On the second aspiration, performed two days later, the fluid appeared definitely serosanguinous. The question remains whether this sanguinous character of the fluid was due to trauma or whether the severity of the pleuritis, evidenced by the prolonged high temperature, was responsible for the formation of a hemorrhagic exudate.

Of the remaining four cases of tuberculous pleural effusion, only one was associated with the ordinary chronic type of pulmonary tuberculosis. This was a case of chronic bilateral apical tuberculosis with a negative sputum, but a positive guinea-pig test after injection of the fluid. Of the three others, two were cases of polyserositis with *bilateral* pleural effusions and pericarditis. One of these two later developed evidence of pulmonary tuberculosis. The other was proved by the guinea-pig test. The following is a brief summary of these two cases:

Case 1. A case of bilateral pleurisy and pericarditis in a young Puerto-Rican. The illness began with fever, cough, and hemoptysis. At first, bilateral pulmonary infiltrations were seen in the roentgen-ray film. Several examinations of the sputum for tubercle bacilli were negative. The guinea-pig test of the fluid was positive. After the pulmonary signs had subsided, the patient developed marked enlargement of the liver, and an increase in venous pressure to 17 centimeters. He recovered after six weeks, and subsequent roentgen films showed the pulmonary infiltrations to have been largely absorbed. Two years later, the patient showed active pulmonary tuberculosis with positive sputum.

Case 2. A case of tuberculous polyserositis proved by a positive guinea-pig test, in a man who also had coronary arteriosclerosis and arterial hypertension. Hemorrhagic fluid was obtained from the pleura on the second of six aspirations.

The eighth case of tuberculous pleural effusion occurred in a patient suffering from Laennec's cirrhosis of the liver with ascites. The diagnosis was proved by postmortem examination. The tuberculous etiology of the large pleural effusion was established by the guinea-pig test. That cirrhosis of the liver in itself may give rise to hemorrhagic pleural effusion has been repeatedly reported in the literature, e.g. by Christian.⁹

I have not observed any hemorrhagic pleural effusions in cases of rapidly advancing pulmonary tuberculosis of the exudative type, nor in cases of acute miliary tuberculosis.

The amount of fluid found in the tuberculous cases—those of polyserositis excepted—was usually smaller than that encountered in the cases of neoplasm, and massive hemorrhagic effusions which covered the lung from apex to base were not seen. The number of leukocytes was below 1000 in five of the six cases in which it was counted, 2000 in the sixth. Lymphocytes greatly predominated in all eight. The specific gravity of the fluid

(cases of polyserositis excepted) was above 1.018, save in one idiopathic effusion, where it was 1.012.

To sum up this group, it may be stated that in my experience, hemorrhagic pleural effusions of tuberculous origin are not very common. They were found to occur in five types:

- | | |
|------------|---|
| Unilateral | { 1. As the first clinical manifestation of tuberculosis, the equivalent of so-called "idiopathic" serofibrinous pleural effusions. |
| | { 2. As tuberculous hemopneumothorax. |
| | { 3. In the course of chronic pulmonary tuberculosis (only one case seen). |
| | { 4. In association with Laennec's cirrhosis of the liver. |
| Bilateral | As part of tuberculous polyserositis. |

Miscellaneous Inflammatory Conditions. This series includes 13 cases of non-tuberculous inflammatory conditions which caused a hemorrhagic pleural effusion. In most of these cases, the effusion was but one manifestation of a violent systemic infection.

A. Sepsis. This infection took the form of a sepsis in the following four cases.

Case 1. A case of hemorrhagic bronchopneumonia and sepsis. Pneumococcus type 3 and *Streptococcus hemolyticus* were grown on blood culture. The infection was so fulminating that the patient died within one day. At postmortem examination, a bilateral pleural effusion was found with 500 c.c. of serosanguinous fluid in each side of the chest.

Case 2. A case of hemorrhagic pleural effusion (1800 c.c.) with fever and sweats of 17 days' duration, then sudden drop of temperature to approximately normal. Sputum was copious; numerous examinations for tubercle bacilli were negative. A few small infiltrations in each infraclavicular region were seen in the roentgen-ray film. The guinea-pig test of the pleural fluid was negative. The fluid contained 50 per cent polymorphonuclears. On blood culture, *Streptococcus hemolyticus* was grown in one flask.

Case 3. Left-sided hemorrhagic pleural effusion in a 2 year old child suffering from acute bacterial endocarditis with *Staphylococcus aureus* sepsis. At necropsy, areas of bronchopneumonia were found in both lungs, also multiple hemorrhages of skin, nose, mouth, and kidney.

Case 4. A 17-day-old infant with acute intestinal intoxication. Here a *Bacillus coli* sepsis was proved by the finding of *Bacillus coli* in cultures from the blood, the lung, and an ear abscess. Confluent bronchopneumonia of the left upper and lower lobes as well as small abscesses of the pleura were found at postmortem examination.

It is well known that sepsis frequently causes damage to blood vessels and thus gives rise to hemorrhage. Two of the four patients just described showed evidences of hemorrhagic tendency by bleeding in various other parts of the body. It is, therefore, not surprising that the pleural effusions of these septic patients should have been hemorrhagic. While all of these four cases also had bronchopneumonia, there seems little doubt that the sepsis and not the pneumonia was the principal cause of the hemorrhagic effusion.

B. Lobar Pneumonia. There were, however, six cases of hemorrhagic pleural effusion in which pneumonia, but no sepsis was found. Only two of the six were cases of lobar pneumonia, one due to type 2, the other to group 4 pneumococcus. In both, the pleural effusion was very small (only 20 c.c. and 75 c.c. respectively were aspirated) and of little clinical significance. Trauma may have caused the hemorrhagic character of the fluid in one or both of these cases as trauma is apt to occur when there is a very small amount of fluid. In any event, hemorrhagic pleural effusion is certainly a rare complication of lobar pneumonia and one of minor importance.

C. Bronchopneumonia. In four cases of this series, bronchopneumonia was associated with hemorrhagic pleural effusion, without sepsis being present. Two of these patients were luetics.

Case 1. A case of bilateral hemorrhagic bronchopneumonia and a very small hemorrhagic pleural effusion on the right side in a patient suffering from secondary lues. The illness began immediately after an injection of neoarsphenamine.

Case 2. A case of gripple pneumonia in a person suffering from secondary lues. Only 20 c.c. could be aspirated.

Lues may play a part in producing hemorrhagic pleuritis. In the first case, however, the clinical picture is more likely to have been the result of a severe reaction to neoarsphenamine. This drug is known to cause injury to capillaries, and the hemorrhagic character of the effusion may be so explained.

The remaining two cases of bronchopneumonia associated with hemorrhagic pleural effusion did not occur in luetics, but had other unusual features.

Case 3. A case of recurrent bilateral bronchopneumonia of unknown etiology, with bilateral pleural effusions. For five months the pleural fluid was clear, then it became serosanguinous; eventually, it was absorbed. Spirillae were found in the patient's sputum. The disease was accompanied by cough and sputum, and was, therefore, probably a form of interstitial pneumonitis with bilateral pleurisy an essential part of the picture; similar in this respect to atypical interstitial pulmonary infections associated with serous pleurisy, the etiology of which is also unknown.

Case 4. A case of suppurative and hemorrhagic bronchopneumonia, post-measles, in a two year old child; blood culture negative. Two hundred c.c. of fluid were aspirated.

Measles (as well as influenza) is known to produce the suppurative and hemorrhagic type of bronchopneumonia. It is not surprising that such a severe inflammation should have been associated with a pleural effusion of hemorrhagic character.

D. Lung Abscess. In a single case of this series, a hemorrhagic pleural effusion was found to complicate a putrid lung abscess. The abscess had perforated, and adjacent to the empyema, a sympathetic serosanguinous effusion was found. It should be noted, however, that anaerobic streptococci were grown on culture from the effusion.

If we omit from consideration the sympathetic effusion adjacent to a perforated lung abscess, we see that in 7 of the 10 cases of miscellaneous

inflammatory conditions so far discussed, small amounts of fluid (20 to 200 c.c.) were encountered; in two, 500 to 900 c.c. were found, and only one had a large effusion. In four cases, the leukocytes in the effusion were counted. In two, 4000 white cells per cu. mm. were found, in the two others, 500 and 1000 respectively. On the whole, the number of leukocytes was higher than in the tuberculous group. More striking were the results of the differential cell count of the leukocytes in the fluid. From 18 to 96 per cent of polymorphonuclears were found in the five cases where such a count was made. The high percentage of polymorphonuclears distinguishes this group from others, e.g. from the tuberculous effusions.

E. Polyserositis. In addition to the two cases of polyserositis of tuberculous origin which were discussed before, this series includes two more cases of polyserositis.

Case 1. A case of bilateral hemorrhagic effusion and pericarditis in a patient with active rheumatic fever and chronic rheumatic heart disease. In the absence of congestive failure, the effusions were considered inflammatory, as part of a generalized polyserositis, probably of rheumatic origin. Specific gravity of the fluid was 1.014 on one occasion, 1.015 on another.

Case 2. A case of bilateral hemorrhagic pleural effusion with pericarditis. A faint infiltration in the left lung as seen by roentgen-ray suggested pulmonary inflammatory disease as well. The patient coughed for two years, one year under observation. The effusion was definitely inflammatory (specific gravity 1.020), leaving marked pleural thickening as residuum. This was a case of polyserositis, probably Pick's disease (liver 4 fingers below costal margin) in an early stage, in which the pulmonary inflammation was only part of the process. Cause unknown.

In both these cases, the effusions were bilateral and were of large size (1200 c.c. were aspirated from each case). The white cell count (4400 and 2600 leukocytes respectively) was higher than in the two cases of tuberculous polyserositis, and the number of polymorphonuclear cells found in the differential count (50 per cent and 80 per cent respectively) was much higher.

The occurrence of four cases of polyserositis (the two tuberculous cases included) in a series of 120 cases shows that polyserositis is not a very uncommon cause of hemorrhagic pleural effusion, a fact which may not be generally known.

Uremia with Cardiac Failure. A very large effusion of low specific gravity occurred in a patient suffering from hypertensive heart disease. The patient also had lues. He was in uremia, as evidenced by progressive nitrogen retention. There were associated gastric hemorrhages. In this case, the hemorrhagic character of the fluid could be ascribed to the bleeding tendency caused by the uremic state, in addition to the congestion of the lungs due to heart failure.

Pulmonary Embolization. In 10 cases a hemorrhagic pleural effusion was the result of pulmonary embolization.* This is a type of effusion which

* In addition to these ten hemorrhagic effusions, eight serous pleural effusions (not transudates) resulting from pulmonary embolization were seen on the wards of the Mount Sinai Hospital during the years 1928 to 1938.

is not uncommon, but less well known and frequently overlooked.¹⁰ The following is a brief summary of these cases:

Case 1. A case of rheumatic heart disease, mitral stenosis, mitral insufficiency, in very mild congestive failure, showed a collection of serosanguinous fluid localized in the fissure between the right middle lobe and right lower lobe. The fact that the effusion was so localized, the high specific gravity of the fluid (1.016), the presence of fever, and the absence of gross signs of congestive failure in the lungs or liver, all made it appear unlikely that the effusion was a transudate. At postmortem examination, a pulmonary infarct was found in the right middle lobe (and left lower lobe). The patient had never had chest-pain or hemoptysis.

Case 2. A case of rheumatic heart disease, mitral stenosis, mitral insufficiency with auricular fibrillation, in congestive failure. Because of the presence of fever and leukocytosis, and because the effusion was loculated, it was assumed that it did not represent a transudate, although the specific gravity was 1.010 on one occasion, 1.016 on another. That the patient had an infarction of the right lower lobe was made probable by a history of acute pain in the right chest and hemoptysis, also by repeated occurrence of embolic phenomena in the brain. Patient died. Permission for post-mortem examination was not obtained.

Case 3. A case of rheumatic heart disease, mitral stenosis, aortic insufficiency with evidence of pulmonary embolization (hemoptysis), had a bloody effusion from which *Streptococcus viridans* was cultured. Repeated roentgen examinations showed an area of consolidation in the lung in addition to chronic pleural effusion. The case is one of pulmonary infarction with hemorrhagic effusion. The latter was contaminated with *Streptococcus viridans* probably as a result of infection in the infarct.

Case 4. A case of rheumatic heart disease, mitral stenosis, with bilateral large, frequently recurring bloody effusions of low specific gravity. On one examination a friction rub, possibly pericardial, was heard. Patient died; no postmortem examination was performed. It is impossible to state definitely whether the blood in the effusions was secondary to infarcts or to diapedesis from the congested lung.

Case 5. A case of rheumatic heart disease with frequently repeated hemoptyses and jaundice, developed a bloody effusion of high specific gravity (1.020). On two occasions, areas of consolidation were noted on roentgen examination. Infarcts were found at postmortem examination.

Case 6. A 52-year-old male in congestive failure due to coronary artery disease, entered the hospital with a large hemorrhagic pleural effusion having the characteristics of a transudate (specific gravity 1.010). Two weeks after the aspiration of the fluid, roentgen examination of the chest showed an area of consolidation in the right upper lobe. There was no fever, and no cough or expectoration. Although the patient had no hemoptysis, there was little doubt that the area of consolidation was an infarct.

Case 7. Hypertensive heart disease of unusual nature with recurrent bouts of heart failure for eight years. At post mortem, the heart was diffusely dilated and scarred without any gross narrowing of the coronary vessels. There was a history of hemoptysis three months before the first admission, when an area of consolidation in the lung was noted roentgenologically, in addition to the bloody pleural effusion. Four months later, a bloody effusion was still present. After aspiration, an infiltration in the right lower lobe was again noted. At post mortem, eight years later, no lesion was found in the lung. However, the onset with hemoptysis and the roentgen finding of a persistent area of consolidation within the lung justify the assumption that an infarct had been present.

Case 8. A case of essential hypertension and coronary artery disease with marked left ventricular enlargement. The onset of the illness, with pain in the chest, the

recurrence of chest-pain and hemoptysis after getting out of bed, the presence of fever and leukocytosis, and an increased blood sedimentation rate, all suggested multiple pulmonary emboli as the cause of the bilateral pleural effusion. The finding of an enlargement of the right femoral vein with a large lymph node in Scarpa's triangle pointed to a phlebitis as the possible source of the emboli. That the effusion was not a transudate was indicated by the specific gravity (1.020) and by the absence of other signs of congestive heart failure.

Case 9. The sudden occurrence of fever, chest pain and hemoptysis in a patient who had begun complaining of painful external hemorrhoids five days earlier, strongly suggested pulmonary embolization, with the hemorrhoidal veins as the source. The so-called inflamed hemorrhoid later proved to be a perianal abscess spontaneously discharging pus. The pleural fluid at first contained 75 per cent polymorphonuclears, later 100 per cent lymphocytes. The pleural effusion was of moderate size. There were roentgen-ray signs of an underlying lesion in the right lower lobe. This lesion later cleared up completely.

Case 10. A case of malignant nephrosclerosis, with death in uremic coma. At postmortem, the axillary portion of the left lower lobe showed a cavity within an infarct. The cavity had perforated, resulting in a hemorrhagic pleural effusion. The branch of the pulmonary artery leading to the infarct contained a riding embolus. The source of the embolus was not demonstrated.

Thus, eight of the ten cases of pulmonary embolism were cardiacs; five were cases of valvular heart disease, two were cases of coronary sclerosis in heart failure, and one a case of hypertensive heart disease in heart failure. In such cases, conditions favoring hemorrhagic infarction usually exist. It is, therefore, not surprising that the pleural effusion overlying the infarction should have been hemorrhagic. Only two cases of this group were non-cardiacs. In one of these, the source of the embolus presumably was a phlebitis of the hemorrhoidal veins; in the other, the case of malignant nephrosclerosis (number 10), the source of the embolus remained undetermined. The pleural effusions in most of these cases were of large size, often requiring numerous aspirations. The fluid was always serosanguinous, never "pure blood." The white cell count in the fluid, which was made in nine of the ten cases, was below 1000 in eight instances, and the white cells were almost all lymphocytes, except in the patient suffering from pararectal abscess, where 75 per cent polymorphonuclears were found.

Pelvic Fibromatous Tumors. A small group of cases, but one to which unusual interest is attached, consists of two cases * of hemorrhagic pleural effusion secondary to pelvic fibromatous tumors. This syndrome, until recently unknown, has been established as a clinical entity by the reports of Hoon, Salmon, Meigs and Cass, and Weld.¹¹ Of the cases included in this series, one had a fibroma of the right ovary, the other fibromyomata of the uterus. Both had ascites and large right-sided bloody pleural effusions, which disappeared following operative removal of the pelvic tumors. In both cases, the fluid failed to show tumor cells on repeated examination. In the one patient where a cell count was made and the specific gravity tested, the

* The two cases included in this series are the same which Salmon¹¹ has reported in detail. Salmon's third case as well as the other 14 cases reported in the literature had serous pleural effusions.

fluid contained 920 white blood cells per cu. mm., 92 per cent of which were lymphocytes; the specific gravity was 1.020. Both patients are now well. The manner in which the pelvic tumors led to the development of the pleural effusions is obscure. Rabin¹² has suggested that this type of pleural effusion might also be caused by pulmonary embolization.

Leukemia and Hodgkin's Lymphogranulomatosis. Two cases of chronic lymphatic leukemia and one case of lymphogranulomatosis were included in this series. The following is a brief description of these three cases.

Case 1. A case of chronic lymphatic leukemia in a 63-year-old woman who showed petechiae in the mouth, pharynx, skin, and retina. The platelet count was only 30,000. The effusion was bilateral. On the right side, it was very large and reaccumulated rapidly. The fluid contained 54,000 white blood cells, nearly all small lymphocytes. The patient died; permission for postmortem examination was not obtained.

Case 2. Bilateral serosanguinous pleural effusion in a case of chronic lymphatic leukemia with large mediastinal growths. On the right side, the effusion was of very large size and reaccumulated rapidly after aspirations. The fluid contained 65,000 white blood cells, 99 per cent of which were lymphocytes. The patient later developed cutaneous, conjunctival, and gastric hemorrhages, and his platelet count which had been normal, dropped to 60,000. The patient died; permission for postmortem examination was not obtained.

Case 3. A case of lymphogranulomatosis, proved by biopsy of a cervical gland. The patient had a very large effusion on the right side, and the roentgen-ray film also showed a small effusion on the left side. Four thoracenteses were performed within nine days. The first three aspirations yielded serosanguinous fluid, the fourth yellow, turbid fluid. The fluid contained only 500 white blood cells per cu. mm., 56 per cent of which were polymorphonuclears and 44 per cent lymphocytes. The patient showed no other signs of bleeding tendency. The patient died; permission for postmortem examination was not obtained.

Hemorrhagic tendencies are characteristic of lymphatic leukemias, and it is therefore easily understood that pleural effusions developing during their course should have been hemorrhagic. In both cases of leukemia, there were hemorrhages of other organs, and both had a low platelet count. A characteristic feature of both cases was the finding of very large numbers of lymphocytes in the pleural fluid. I have not found any other type of effusion with a similarly high number of lymphocytes.

Lymphogranulomatosis, on the other hand, is not characterized by bleeding tendencies. At the Mount Sinai Hospital, a considerable number of cases of this disease has been observed, but the case reported here is the only one associated with a hemorrhagic pleural effusion.

In all three cases, the effusions were bilateral and were as massive as those due to malignant neoplasm commonly are. They also reaccumulated rapidly after each thoracentesis.

Diagnosis Undetermined. There were five cases in which the nature of the pleural effusion remained undetermined.

Case 1. A 43-year-old man with a hemorrhagic effusion of short duration. The effusion disappeared within three weeks after aspiration. Unusual features of the case

were a hemoptysis, and the fact that the fluid contained 30 per cent eosinophiles. Guinea-pig inoculations were negative for tuberculosis. Roentgen-ray examination after the disappearance of the effusion showed no evidence of a tuberculous lesion in the lungs. The hemoptysis and the pleural effusion should, therefore, be explained on some basis other than tuberculosis.

Case 2. A hemorrhagic pleural effusion showing 89 per cent lymphocytes in a boy of 16, associated with fever, congested pharynx, cough with purulent sputum, and a submaxillary abscess. Pleural fluid was negative for tubercle bacilli on guinea-pig inoculation and Loewenstein culture. Two guinea-pigs inoculated with pus from the submaxillary abscess died within 12 and 14 days, respectively, without evidence of tuberculosis. In the absence of proof, the case cannot be considered tuberculous; the symptoms suggest an infection beginning in the throat and descending into the pleura.

Case 3. A 44-year-old man entered the hospital with signs of polyneuritis of the extremities, leukocytosis of 41,200, and a serosanguinous effusion in the left pleural cavity. The effusion, which was lymphocytic, did not reaccumulate after two aspirations. Roentgen-ray showed a coarse shadow in the left lower lobe. Subsequent films showed gradual disappearance of this shadow. The patient lived for two and a half more years, during which the signs of polyneuritis gradually improved and pulmonary symptoms remained absent. He had essential hypertension and died of acute coronary thrombosis at another institution. While it is impossible to determine the cause of the pleural effusion, it can be definitely stated that it was not neoplastic.

Case 4. A mildly hemorrhagic effusion (4700 red blood cells per cu. mm.) persisting over a period of four months, associated with low grade fever (up to 101, rarely to 102 degrees), anemia (hemoglobin 40 to 60 per cent), and arthritis. The joints contained grumous material. The effusion was evidently part of a generalized inflammatory disease, the nature of which is unknown. Although the Mantoux test was positive in a dilution of 1:100,000 and although there developed a symmetrical fusiform swelling in two toes, two guinea-pig inoculations with the pleural fluid and one with the joint-fluid were negative for tubercle bacilli.

Case 5. A case of luetic aortic insufficiency in congestive heart failure. The fact that the hemorrhagic pleural effusion was encapsulated in the right lung fissure suggested that it might not be a transudate. The specific gravity of the fluid was not determined. In the absence of chest-pain, hemoptysis, fever, and leukocytosis, there is no evidence that the patient had an infarct of the right lower lobe. The patient died. Postmortem examination was not made.

While the cause of the pleural effusion in these five cases remained obscure, one may be reasonably certain that they were not due to neoplasm. It seems fair to assume that the effusion in most, if not in all of them, was inflammatory in origin.

Conditions Not Occurring in This Series. A number of other conditions which are described in the literature as causes of hemorrhagic pleural effusion did not occur in this series. They are typhoid fever (Gasparini¹³ Piana³), paratyphoid B infection (Bollettini¹⁴), malaria (Zimine¹⁵), rheumatic fever, anthrax, bubonic plague, scurvy, purpura, hemophilia (Lauche¹⁶) icterus, severe anemia (Kaufmann¹⁷), small-pox (Beitzke¹⁸), and nephritis (Lord⁵).

SUMMARY

1. One hundred and twenty cases of hemorrhagic pleural effusion, exclusive of six cases of spontaneous hemopneumothorax, were analyzed.

2. Seventy-eight cases (65 per cent) were due to malignant neoplasm.

a. In 77 of these, the neoplasm was metastatic.

b. In half of these cases, the primary neoplasm was in the lung, and in the remainder it was in other organs.

c. In only one case was the tumor primary in the pleura.

d. Tumor cells were found in 50 per cent of the hemorrhagic effusions examined, which was the same frequency as that observed in non-hemorrhagic neoplastic effusions.

3. Forty-two cases (35 per cent) were due to various other causes, viz.

a. miscellaneous inflammatory conditions (13 cases)

α sepsis

β lobar pneumonia

γ bronchopneumonia

δ lung abscess

ε polyserositis

b. tuberculosis (8 cases)

c. pulmonary embolization (10 cases)

d. pelvic fibromatous tumors (2 cases)

e. leukemia (2 cases)

f. Hodgkin's lymphogranulomatosis (1 case)

g. uremia associated with cardiac failure (1 case)

h. undetermined causes (malignant neoplasm excluded) (5 cases).

4. Tuberculous hemorrhagic pleural effusions were infrequent (8 cases). Four of these appeared as "idiopathic" pleural effusions, two as part of a tuberculous polyserositis, one in association with cirrhosis of the liver, and only one was associated with chronic pulmonary tuberculosis.

5. The frequency of the various types of polyserositis as a cause of hemorrhagic pleural effusion (four cases) is noteworthy.

6. A hemorrhagic effusion may be the sole evidence of a hidden pulmonary embolus.

7. The determination of the percentage of polymorphonuclears and lymphocytes in the fluid does not aid in differentiating between malignant and inflammatory conditions of the pleura. The two cases of hemorrhagic effusion due to lymphatic leukemia were characterized by lymphocytic counts much in excess of all other cases in the series.

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REFERENCES

1. KOROL, E.: Hemorrhagic pleurisy of tuberculous origin and hemopneumothorax, *Am. Rev. Tuberc.*, 1936, xxxiii, 185.
2. TAILLENS: Hemorrhagic pleurisy in children, *Schweiz. med. Wehnschr.*, 1938, lxviii, 1133.

3. PIANA, G. A.: Hemorrhagic pleurisy—various forms in children, *Clin. Pediat.*, 1934, xvi, 569.
4. NORRIS, G. W., and LANDIS, H. R. M.: *Diseases of the chest*, fourth edition, 1929, W. B. Saunders Co., Philadelphia, pp. 680-681.
5. LORD, F. T.: *Diseases of the bronchi, lungs and pleura*, Second edition, 1925, Lea & Febiger, Philadelphia, p. 692.
6. MONTAGU, A.: *Les pleurésies hémorrhagiques*, Thesis, Paris, 1919.
7. (a) DIEULAFOY, quoted by Norris and Landis.⁴
 (b) DIEULAFOY: *Des pleurésies hémorrhagiques*, *Gazette Hebdomadaire de Med. et de Chir.*, 1885, xxxii, 271.
8. (a) MANDLEBAUM, F. S.: The diagnosis of malignant tumors by paraffin sections of centrifuged exudates, *Jr. Lab. and Clin. Med.*, 1917, ii, 580.
 (b) ZEMANSKY, A. P., JR.: The examination of fluids for tumor cells, *Am. Jr. Med. Sci.*, 1928, clxxv, 489.
 (c) GOLDMAN, A.: Cytology of serous effusions, with special reference to tumor cells, *Arch. Surg.*, 1929, xix, 1672.
9. CHRISTIAN, H. A.: Hemorrhagic pleurisy—an unusual complication of cirrhosis of liver, *Trans. Assoc. Am. Phys.*, 1937, lii, 167.
10. (a) MILLER, G. B.: The significance of post-operative pleurisy; its relation to pulmonary embolism, *Am. Med.*, 1902, iv, 173.
 (b) GSELL, O.: *Der hämorrhagische Lungeninfarkt und seine Komplikationen*, *Deutsch. Arch. f. klin. Med.*, 1935, clxxvii, 475.
11. (a) HOON, M. R.: Fibromata of the ovary, *Surg., Gynec. and Obst.*, 1923, xxxvi, 247.
 (b) SALMON, U. J.: Benign pelvic tumors associated with ascites and pleural effusion, *Jr. Mount Sinai Hosp.*, 1934, i, 169.
 (c) MEIGS, J. V., and CASS, J. W.: Fibroma of the ovary with ascites and hydrothorax; with a report of 8 cases, *Am. Jr. Obst. and Gynec.*, 1937, xxxiii, 249.
 (d) WELD, S. B.: Fibroma of the ovary with ascites and pleural effusion, *New England Jr. Med.*, 1938, ccxviii, 262.
12. RABIN, C. B.: Personal communication.
13. GASPARINI, A.: Primary bilateral hemorrhagic pleurisy from Eberth's bacillus, *Gazz. d. Osp.*, 1930, li, 239.
14. BOLLETTINI, A.: Hemorrhagic pleurisy due to paratyphoid B infection, *Riv. Di Clin. Pediat*, 1934, xxxii, 40.
15. ZIMINE, E.: Hemorrhagic pleurisy of malarial origin, *Bull. Soc. Path. Exot.*, 1936, xxix, 267.
16. LAUCHE, A.: Hemorrhagic pleurisy, in HENKE-LUBARSCH, *Handbuch der speziellen pathologischen Anatomie und Histologie*, vol. 3, part 1, p. 883.
17. KAUFMANN, E.: *Lehrbuch der speziellen pathologischen Anatomie*, Berlin and Leipzig, 1922, vol. 1, p. 381.
18. BEITZKE, H., in ASCHOFF, L.: *Pathologische Anatomie*, fourth edition, Jena, 1919, vol. 2, p. 367.

ANTACIDS: THEIR EFFECT BY TITRATION AND WITHIN THE HUMAN STOMACH *

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OF the various forms of treatment used in peptic ulcer, acid neutralization therapy has held the most prominent position for over one hundred years. In the quest for a better antacid many substances have been tried but no ideal agent has been found. Many virtues have been attributed to these compounds but as far as is known their chief value lies in their acid reducing property. We have, therefore, made analyses of some of the more commonly used substances on a basis in which their neutralizing capacity by titration can be compared with their antacid property within the human stomach.

It has been repeatedly shown that the amounts of acid and other gastric secretions vary, not only in different individuals but also from time to time in each subject. Careful work by Hollander¹ seems to corroborate Pavlov's theory that the concentration of acid secreted is constant but the amount produced varies. Although no pure parietal secretion has been obtained, it has been calculated that a concentration of 0.17 N HCl, isotonic with blood, is formed.² No gastric concentration greater than this has been found and it is plausible that all lesser concentrations are due to dilution or buffer substances. Most antacids are evaluated in terms of 0.10 N or 0.05 N HCl. If a physiologic basic is desired, we believe it should be made in terms of pure parietal secretion.

Neutrality should be defined unless a truly neutral solution is meant. Only at pH 7, when both hydrogen and hydroxyl ions are in equilibrium, do we have a neutral solution. Frequently neutrality is implied when a solution is neutral to a given indicator, such as Toepfer's reagent which has a range from pH 2.9 to 4. If other dye indicators are used their pH range should be kept in mind.

As far as gastric acid reduction is concerned, pH 7 is unnecessary since practically no pepsin activity is seen above pH 5. The free acidity end point is pH 3.5 and that of total acidity pH 7. Hollander³ has designated pH 5 as the proteolytic neutralization point. Pepsin activity follows a bell-shaped curve as the hydrogen-ion concentration is increased; optimum action on most proteins occurs between pH 1.5 and 2.5 and decreases after that point is reached.

In a previous study we were unable to measure any egg white digestion in the stomach when its contents were maintained at pH 3.5 or higher, over

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From the Gastro-Intestinal Departments of Presbyterian Hospital and Rush Medical College.

a three hour test period. From our experience it seems unlikely that pH 5, desirable as it may be, is frequently attained or maintained in antacid therapy and therefore we believe that pH 3.5 within the stomach should be considered sufficient at the present time.

METHOD OF PROCEDURE

Toepfer's reagent (dimethyl-amino-azobenzene) is the most commonly used dye indicator in titrating gastric contents. This dye is bright red at pH 2.9 and yellow at pH 4.0. In clear solutions accurate titrations can be made but colored or opaque media make it difficult to estimate a uniform end point. Recent improvements in electrometric measurement of pH with a glass electrode make it possible to determine acid values easily and accurately. For these reasons we made all measurements with a Coleman electrometer, using a glass electrode.

In the titrations, two grams of dry or 10 c.c. of liquid were used as standard amounts of test substance. These were dissolved or diluted in 150 c.c. of distilled water, a reading taken and 0.17 N HCl added in 2 c.c. amounts. The titration flask was stirred continuously and a reading taken after each addition of acid. Most substances gave an immediate constant reading. Slowly acting antacids were tested by adding 30 c.c. of acid at one time and taking readings at five minute intervals for 30 minutes.

In testing the reaction within the human stomach a special^{4, 5} glass electrode was placed in the antrum. Patients without organic gastrointestinal pathology were chosen. Ninety cubic centimeters of milk and antacid were given individually at alternate half-hour intervals. No other medication was given. The electrode was lowered into a fasting stomach, ulcer management begun and in 30 or more minutes test readings were started. In each instance readings were taken at five minute intervals over a two hour period.

RESULTS

BY TITRATION

Magnesium Salts. In table 1 the tremendous neutralizing capacity of magnesium is apparent. The oxide is more than twice as effective as calcium carbonate, its closest rival, but its use is limited because of its laxative

TABLE I

The comparative neutralizing capacity of equal amounts of commonly used antacid powders as determined by titration

*Comparative Neutralizing Values * of Inorganic Antacids*

10 gr. (.66 gm.) Magnesium Oxide.....	81.8 c.c.
10 gr. (.66 gm.) Calcium Carbonate.....	37.4 c.c.
10 gr. (.66 gm.) Sodium Bicarbonate.....	23.3 c.c.
10 gr. (.66 gm.) Tribasic Calcium Phosphate.....	20.6 c.c.
10 gr. (.66 gm.) Tribasic Magnesium Phosphate.....	16.6 c.c.
10 gr. (.66 gm.) Magnesium Trisilicate (Trisomin).....	30.0 c.c. (30 min.)
10 gr. (.66 gm.) Bismuth Subcarbonate.....	almost 0.

* Amount of .17N HCl required to titrate equal weight of antacids to pH 3.5.

property. It is employed chiefly in combination with sodium bicarbonate (table 2) as a laxative in ulcer management. An attempt has been made to take advantage of this antacid property in magnesium trisilicate. This substance acts both chemically and physically by adsorption. The adsorptive action is very slow and its chief reaction is chemical to form magnesium chloride (MgCl_2). Normally the trisilicate is very stable and quite inert unless specially prepared. If used in tablet or capsule form its opportunities

TABLE II

The comparative neutralizing capacity of the usual amounts of antacids used in ulcer therapy

*Neutralizing Capacity of Usual Amounts of Antacids **

10 gr. (.66 gm.) Sodium Bicarbonate	}	105.3 c.c.
10 gr. (.66 gm.) Magnesium Oxide		
20 gr. (1.3 gm.) Tribasic Calcium Phosphate	}	66.2 c.c.
15 gr. (1.0 gm.) Tribasic Magnesium Phosphate		
15 gr. (1.0 gm.) Calcium Carbonate		56.1 c.c.
3 oz. (90 c.c.) Whole Regular Milk		39.7 c.c.
3 oz. (90 c.c.) Half Milk and Half Cream (22%)		37.0 c.c.
10 gm. Mucin		54.4 c.c.
10 c.c. Aluminum Hydroxide (Amphojel)		30.0 c.c. (in 7 to 10 min.)
10 gr. (.66 gm.) Magnesium Trisilicate (Trisomin)		30.0 c.c. (in 30 min.)

* Amount of .17N HCl required to titrate the antacid to pH 3.5.

for reaction are delayed further. To bring out its optimum action only the powder form was used. Even in that state its action was slow and thirty minutes passed before 30 c.c. of 0.17 N HCl were brought to pH 3.5 by 10 grains of this antacid.

Calcium Carbonate. This powder is one of the oldest and best known antacids. It is very effective in speedy acid reduction and economical (chart 1). Slight solubility has discouraged its use because of a tendency to upset the body chemistry, especially in patients with disturbed renal function. If given frequently, its constipating action must be regulated with a laxative.

Tribasic Powders. We use the tribasic forms of calcium and magnesium phosphate extensively. Their limited neutralizing capacity is made up by giving larger doses. Usually a combination of 20 grains of calcium and 15 grains of magnesium is used. Such a combination not only produces satisfactory acid reduction (table 1) but in most instances allows normal bowel action. The relationship of calcium and magnesium can easily be adjusted to suit the required acid reduction and bowel function when necessary. The extreme insolubility of these salts reduces the likelihood of alkalosis, and very few patients show any idiosyncrasy to them.

Sodium Bicarbonate. Cheapness and availability have made this salt one of our best known antacids. It is satisfactory for occasional use but must not be taken at frequent intervals because of its capacity to disturb the acid-base balance of the body (chart 1).

Bismuth Subcarbonate. This substance is a frequent ingredient of antacid powders. It is merely included to show that it has practically no neu-

tralizing capacity (table 1). Formerly it was thought to have a special affinity for an ulcerated surface and to produce a protective coating, but many observations have disproved this.

Aluminum Hydroxide. This substance has attained wide popularity by virtue of ease of administration and its non-constipating action. It is said not to disturb the acid-base balance of the body but in certain individuals nausea and upper abdominal discomfort are noted. It acts by chemical decomposition to form aluminum chloride, by adsorption, and it is quite astringent. Unless specially treated it is almost inert. Acid reduction is comparatively slow and six to ten minutes are required for 10 c.c. of the usual liquid preparation to bring 30 c.c. of 0.17 N HCl to pH 3.5 (table 2).

Milk. The ability of milk to reduce the corrosive action of gastric juice has kept it prominent in the treatment of gastric disturbances for over one hundred years. It not only neutralizes acid but also provides an excellent source of nutrition; its salts and proteins are the chief acid reducing substances.

TABLE III

Comparative acid reduction of various forms of milk and milk products when titrated against .17 N HCl

*Neutralizing Capacity * of Various Forms of Milk*

I. Liquid Form—(90.0 c.c.)	
Sofkurd.....	41.7 c.c.
Skim-milk.....	41.7 c.c.
Regular Whole Milk.....	39.7 c.c.
Half Milk and half Cream.....	38.2 c.c.
Cream (22%).....	34.2 c.c.
II. Powder Form (9.0 gm.)	
Fat-free Sofkurd.....	45.0 c.c.
Skim-milk.....	42.3 c.c.
Powdered Whole Milk (Klim).....	32.3 c.c.
Sofkurd (Regular).....	31.5 c.c.

* Amount of .17N HCl required to titrate equal amounts of milk to pH 3.5.

Comparative neutralization values of different forms of milk are shown in table 3. One gram of this powder usually equals 10 c.c. of the corresponding liquid form. Liquid Sofkurd, skim-milk and fat-free Sofkurd powder produce the greatest acid reduction. Regular whole milk and a combination of half milk and half cream (22 per cent) are very satisfactory and are commonly used. Increased fat content, as is shown for 22 per cent cream, necessarily reduces neutralizing capacity.

Because fat slows gastric peristalsis and does not aid in acid reduction we are using milk alone rather than a half milk and half cream mixture.

Table 2 is merely included for convenience to show the neutralizing capacity of the usual amounts of antacid used in ulcer therapy.

Gastric Content Neutralization. Characteristic gastric pH values are shown in table 4. These figures represent the average readings obtained at five minute intervals over a two hour test period for patients N. L. B. and A. H. Usual doses of antacid rather than equal amounts of neutralizing

substance were given. By this means an impression is obtained as to the relative effectiveness of each substance within the stomach when given in ordinarily prescribed amounts.

Since the motility, emptying time and amount of acid secreted cannot be known during each test period, we can only compare the results of different antacids with each other and with the fasting state. The neutralizing capacity of the substances used was not equal, yet their proportional acid reduction was not the same.

TABLE IV

Gastric content pH as found when different antacids were used. The total neutralizing capacity of the antacids used in each test is shown

Gastric pH Values

Patient

Test	N. L. B.	A. H.	Antacid's* capacity
Fasting State.....	1.60	1.44	0
Tribasic Calcium Phosphate.....20 gr. (1.3 gm.) Tribasic Magnesium Phosphate.....15 gr. (1.0 gm.)	2.04	4.02	191.8 c.c.
Calcium Carbonate.....15 gr. (1.0 gm.)	1.70	3.28	191.6 c.c.
Sodium Bicarbonate.....20 gr. (1.3 gm.)	2.27	1.92	172.6 c.c.
Aluminum Hydroxide (Amphojel).....10 c.c.	1.81	1.88	139.0 c.c.
Mucin (Armour & Co.).....10 gm.	1.33	1.88	188.2 c.c.
Magnesium Trisilicate (Trisomin).....10 gr. (0.65 gm.)	1.45	2.37	139.4 c.c.
Milk.....3 oz. (90 c.c.)	2.40	2.90	158.8 c.c.

Average pH values of gastric contents of patients N. L. B. and A. H. obtained when readings were taken every 5 minutes over two hour test periods. Except in the fasting state, the test substance was given every hour and 3 oz. (90 c.c.) of milk on the half hour.

* Amount of .17 N HCl required to titrate amount of antacid used during test period, to pH 3.5.

The tribasic powders, calcium carbonate and mucin are equal in neutralizing capacity, yet the first two produced the greatest pH elevation in both patients. These two antacids act quickly, are rapidly diffused and consequently are able to exert their intended effect before leaving the stomach. Mucin, on the other hand, is quite viscid, not readily diffused, and did not produce the desired effect. When titrated in a flask its maximum acid reduction is permitted by vigorous stirring and dilution; gastric peristalses produce less mixture and much of this substance does not come in contact with the gastric secretion.

In the sodium bicarbonate test almost as much neutralizing substance is used as in each of the first three discussed. It is readily diffused, reacts rapidly and yet the average obtained is relatively low; in N. L. B. the highest value was pH 5.48 ten minutes after taking the powder, but in A. H. pH 2.28 was the highest reading obtained at any time during the test.

The neutralizing effect of aluminum hydroxide and magnesium trisilicate has been improved; they react less slowly than formerly, 10 c.c. of the former bringing 30 c.c. of 0.17 N HCl to pH 3.5 in seven to ten minutes, and the latter requiring 30 minutes to accomplish the same result with 10 grains. If an adequate amount of either substance is given and it is retained within the stomach for a sufficient period of time, satisfactory pH elevation should occur. In both instances shown these substances did not produce satisfactory acid reduction.

When 90 c.c. of milk were given every half hour a higher average value was obtained in N. L. B. than when this substance was alternated with another antacid. In patient A. H., the tribasic powder and calcium carbonate tests were the only ones which gave a higher value than when milk alone was used. These results speak very favorably for milk and should be considered in other tests in which it represents 50 per cent of the neutralizing substance.

SUMMARY

A better understanding as to the effectiveness of antacids is needed. This can be accomplished by comparing titration values with those obtained within the stomach. Such neutralization can best be studied by use of a gastric electrode placed in the most acid portion of the gastric content and the amount of acid reduction frequently determined. By this means continuous values may be obtained and the gastric content is not disturbed. If the stomach functioned as a churn and the acid content were the same in all portions, aspiration samples could be used; but since there is a marked difference in degree of acidity in different regions, such samples are not satisfactory. Furthermore, aspiration changes volume, and arrangement of the stomach content and frequent removal of material alter the usual state of affairs.

An antacid to reduce the gastric acidity must be readily diffused, act promptly, and be given frequently in adequate doses. Viscid substances, tablets or capsules, prevent rapid diffusion and thus even a potent antacid may leave the stomach before being able to exert its intended effect. The same holds true for slowly acting substances; unless there is gastric retention an antacid must act within thirty minutes or less to be effective.

Pure gastric juice has no constant acidity. Since this secretion is a mixture we have chosen the calculated value for the pure parietal secretion, 0.17 N HCl, which apparently is fixed, rather than some arbitrary value.

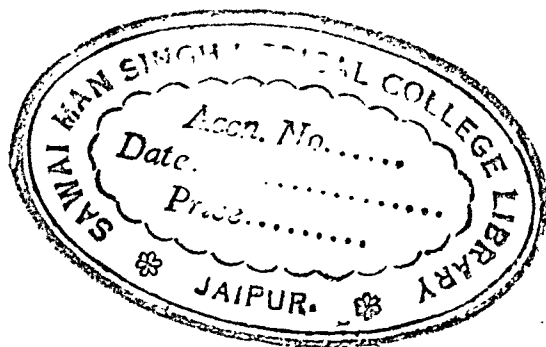
The end point pH 3.5 may later be shown to be incorrect. From our experience in egg white digestion studies and from observations on the acid level usually attained or maintained in antacid therapy, it does not seem likely that a higher value is necessary.

CONCLUSIONS

1. A standard means of antacid evaluation is suggested.
2. The physical as well as chemical properties of antacids should be considered in neutralization therapy.
3. The degree of gastric acid reduction accomplished with an antacid cannot always be predicted from its potential neutralizing capacity as determined by titration.
4. In most instances a surprisingly small decrease in gastric acidity is accomplished even when the customary amount of antacid is given every 30 minutes.
5. Milk is one of our most satisfactory neutralizing agents.

REFERENCES

1. HOLLANDER, F.: The composition of pure gastric juice, *Am. Jr. Digest. Dis. and Nutr.*, 1934, i, 319-329.
2. HOLLANDER, F.: The composition of gastric juice as a function of its acidity, *Jr. Biol. Chem.*, 1934, civ, 33-42.
3. HOLLANDER, F.: What constitutes effective neutralization of gastric contents, *Am. Jr. Digest. Dis.*, 1939, vi, 127.
4. EYERLY, J. B., and BREUHAUS, H. C.: A method of measuring acidity and protein digestion within the human stomach, *Am. Jr. Digest. Dis.*, 1939, vi, 187-191.
5. EYERLY, J. B.: The comparative pH values within the stomach, pylorus and duodenum in antacid therapy. (To be published.)



A NEW TYPE OF GRADUATE COURSE IN INTERNAL MEDICINE *

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THE development in recent years of a steadily mounting demand for graduate training in the specialties, including that of internal medicine, of a sustained and practical sort, quite different from that provided by the usual "refresher" course, has occasioned a search for new types of curriculum. Hospital residencies, to be sure, may provide such training, but with the pressure generated by the various specialty boards the opportunities which residencies provide are inadequate.

To meet the demand in a new way, in the field of internal medicine, the course which we are about to describe was put into operation in the Medical Clinic of the Massachusetts General Hospital in September 1939. The objective was twofold: first, to provide a year of training which would be acceptable as one of the years prescribed by the Board of Internal Medicine; and, second, to increase the man-power of the hospital staff by making use of the professional service of the graduate students.

It is, we believe, the common experience of medical educators that work done by students which carries genuine responsibility in the care of the patient is more stimulating, satisfactory, and indeed educational, than that which is organized without any such responsibility. Internships and residencies are the outstanding type of training by the method of taking responsibility under guidance. The clinical clerkship of undergraduate medical students is another example. In designing the course under discussion the element of responsibility was included insofar as this was possible without disrupting the house staff and undergraduate curriculum. The Out-Patient Department, which is large, provided an opportunity.

The undergraduate student of medicine pays a substantial fee for his instruction. The medical graduate, receiving further training as intern or resident, pays for his instruction by service. Indeed, for the payment which he makes in service he receives not only experience, but also board and lodging and, in the case of residents, a small salary. The graduate course which we have devised occupies a position between these extremes. The graduate student pays for his instruction partly in money, partly in service. The tuition fee has been reduced to a minimum and professional service accepted, so to speak, in part payment for instruction.†

* From the Medical Clinic of the Massachusetts General Hospital and the Harvard Medical School Courses for Graduates.

† The money received in fees is used to pay salaries to those instructors devoting a considerable amount of time to the course, chiefly the tutor in general charge. The payment in service may be looked upon as payment to the clinic for overhead and for a considerable amount of instruction given by many of its staff, without remuneration, as part of their regular routine. That is to say, the graduate student helps the clinic, and in turn the clinic helps the graduate student.

Course No. 240, as it is listed by the Harvard Medical School Courses for Graduates, was preceded by a system under which graduate students had been coming to the hospital individually for a number of years, with a full-time curriculum arranged for each to meet individual needs. The curriculum of Course No. 240 has been modeled in the light of experience gained in the cases of these individuals who came to us before the course was formally organized.

Course No. 240 is of 12 months' duration. It is limited to six doctors. Those selected are carefully chosen. Except for unusual reasons no physician over 35 years of age is accepted. On the other hand, preference is given to candidates who have had at least one year's intern service and have had some experience in the practice of medicine. The candidate should also belong to his local medical society. In addition to these general requirements, letters of recommendation from older physicians are required and in many instances a personal interview is arranged. This gives an opportunity for careful selection while, at the same time, the nature of the course can be explained to the applicant so that he may be sure he is getting just what he wants in the way of training.

Each student spends two mornings a week in the General Medical Clinics of the Out-Patient Department. Here he takes, each morning, two new cases and five to six "old" ones, i.e., patients whom he saw as new ones and has followed since. In this way a moderate-sized practice is conducted over a period of a year. The student has ample time to do complete work-ups and careful follow-ups on all his patients. One of the regular members of the staff is in attendance each day to supervise the work of the graduate students, and since he has only two students each day for whom he is responsible, he has adequate time to go over their cases and discuss diagnosis and treatment with them quite thoroughly. The graduate student's work is done competently, and he is able to see a great many patients in the course of a year under adequate supervision.

In addition to work in the general Out-Patient Department Medical Clinics, as described above, the student is rotated through the various special medical clinics, such as those for diabetes, syphilis, ovarian dysfunction, gastrointestinal, pulmonary and cardiac diseases, etc. The student is given as much free choice as possible as to the clinics in which he will work. It is felt, however, that it is more important to spend a considerable amount of time in certain clinics than a small amount in all. For that reason, a minimum of three months is required in each clinic, one or two days per week. In these clinics the same method pertains. The student works as a regular member of the staff under the supervision of one more experienced.

Each student is assigned to one of the two house medical services on the mornings when he is not in the Out-Patient Department. Here he attends ward rounds with the visiting physician, house staff and undergraduate students. He is given opportunity to observe, to take part in the discussions, to ask questions, and to offer suggestions.

In the normal life of the hospital there are a number of instructive meetings which occur regularly as part of the hospital program. Such exercises are the Medical Grand Rounds, the Clinico-Pathological Conference, the various staff meetings, Research Conference, etc. The student not only has access to all of these, but is urged to attend. This constitutes a valuable part of the training.

The subject of pathology is regarded as one of great importance and to it considerable time is devoted. For a period of three months, one of the members of the pathology staff conducts a concentrated course in pathology three afternoons a week. Not only is gross and microscopic pathology considered, but the clinical histories and physical findings are correlated with the gross and microscopic findings. The instructor also conducts clinico-pathologic exercises each afternoon of the course. In rotation each student is given a clinical history a few days before he is to present it. At the exercise he presents his case and discusses the differential diagnosis. The whole group enters into the discussion, at the conclusion of which the pathologist presents the autopsy findings, and in the light of these, the case is further discussed. At about a third of these exercises the clinical side of the case is presented and discussed by one of the members of the medical staff. In these three months a good comprehensive review of pathology is conducted, with special emphasis on its relation to the practice of internal medicine.

Instruction in certain more specialized subjects is carried on by members of the staff particularly interested in these fields. Thus a course in hematology is given during the afternoons of one month. Not only are lectures given, but the students are required to study the patients and to perform the necessary blood studies on them. A six weeks' course in cardiology, with work in roentgen-ray and electrocardiography, is conducted by one of the members of the cardiac department. Similar work is available in neurology and in arthritis. Other special work may be added as time goes on.

From time to time throughout the year, rounds or talks on special clinical or laboratory subjects are given by various members of the staff working in such special fields.

One of the younger members of the staff is in direct charge of the group, under the supervision of the Chief of the Medical Services. This younger member acts as tutor. He arranges the schedules of the individual student and meets with the group to discuss their work at weekly conferences. A journal club is also organized. Each member of the group is made responsible for certain journals, which he reads and from which each week he presents and discusses articles of significance. This stimulates the students to become familiar with the more recent literature. Topics of special interest are also assigned to each student. The topic is looked up in detail in the standard works and in the recent literature, and presented to the whole group at one of the weekly conferences.

In addition to all these activities, which are more or less organized, the student is encouraged to do considerable reading in the libraries, both at the hospital and outside. He also has access to the wards for study of patients at any time.

From the above description it can be seen that the course is so arranged that the student is able to see a great deal of clinical material in the course of a year and has the time to digest this thoroughly. This clinical experience is supplemented by formal instruction in certain fields which lend themselves to this method, and by reading. In this way we believe a well rounded experience and course of study are presented.

SUMMARY

A new type of graduate course is described. It is designed to give full-time graduate training of a practical nature, in internal medicine, to young physicians who have had internships and who, preferably, have been a few years in general practice. This course serves as a preparation for the practice of internal medicine as a specialty. The principle is introduced of holding the tuition fee at a minimum and of letting the student make part of his payment for instruction in the form of professional service rendered.. A method has been found by which graduate students of this sort can be accommodated in a large teaching clinic without interfering in any way with the work of either the house staff or the undergraduate medical students.

CASE REPORTS

INFLUENCE OF VARIOUS THERAPEUTIC MEASURES ON PERIODIC HEART BLOCK ASSOCIATED WITH CHEYNE-STOKES RESPIRATION; A CASE REPORT*

By HENRY MILLER, M.D., and FRANK T. FULTON, M.D., *Boston, Massachusetts*

THE number of published reports of cyclic disturbances in cardiac rhythm associated with the two phases of Cheyne-Stokes respiration are few. Steele and Anthony¹ in 1933 were able to find but 15 cases including their own and of these only seven were studied by means of electrocardiograms. Since then several additional cases have been recorded in the literature.² It is not the purpose of this communication to review to any extent the literature pertaining to the arrhythmias associated with Cheyne-Stokes respiration but to report the study of an interesting case coming under our personal observation. The effect of various therapeutic measures with specific effects on the circulatory and respiratory systems was ascertained in an effort to obtain a better understanding of the mechanism involved.

CASE REPORT

I. W., a 56-year-old Negro, was admitted to the Rhode Island Hospital on October 9, 1938 complaining of exertional and paroxysmal dyspnea, cough and insomnia. There was a definite history of an untreated penile sore about 20 years previously.

A diagnosis of luetic aortitis was made. The patient improved rapidly on bed rest, digitalis and routine cardiac care and was discharged improved 11 days later. An electrocardiogram (figure 1A) showed marked left axis deviation, prolonged P-R time up to 0.24 second and diphasic T-waves in Lead I.

On November 13, 1938 he was readmitted to the hospital in an attack of acute pulmonary edema. He again improved rapidly on oxygen, bed rest, digitalis and sedatives and was discharged two weeks later. An electrocardiogram (figure 1B) showed a more deeply inverted T₁, a diphasic T₂ and marked left axis deviation. In the precordial lead the T-wave was now inverted.

Following discharge, the patient was fairly comfortable on markedly restricted activity and 1½ grains of digitalis per day until 12 days prior to admission to the hospital at which time he again began to experience attacks of nocturnal dyspnea. Because of the increasing severity of these attacks he was again admitted to the hospital.

Physical examination revealed a well-developed and nourished Negro exhibiting Cheyne-Stokes respiration. The periods of apnea lasted from 20 to 30 seconds and hyperpnea from 45 to 55 seconds. It was noted that the pulse became slow during the apneic periods and increased during the hyperpneic phases. The veins of the neck were congested and showed expansile systolic pulsations. Marked systolic pulsation of the carotid vessels was present. The pupils were unequal and fixed to light; the fundal vessels were moderately arteriosclerotic. A heaving elevation of the entire chest synchronous with each heart beat was evident. Resonance was diminished over the

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From the Heart Station of the Rhode Island Hospital, Providence, Rhode Island.

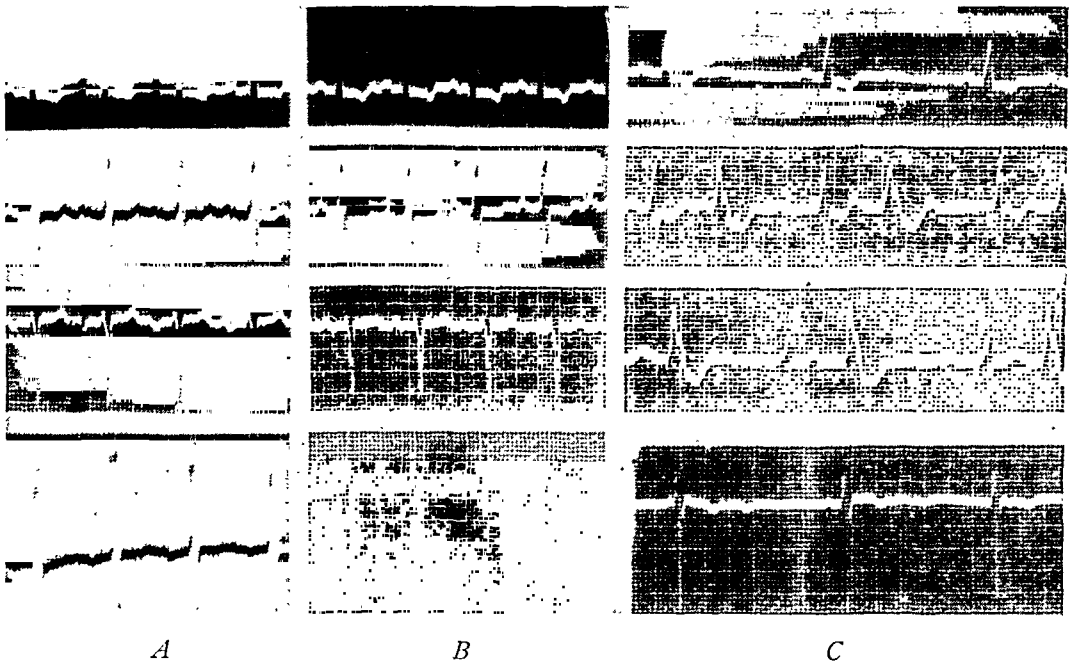


FIG. 1 *A* (Oct. 1938). P-R interval 0.24 sec. Rate 88 per min. *B* (Nov. 1938). P-R interval 0.20-0.22 sec. Rate 94 per min. *C* (May 1939). Leads I and IV—(2:1) partial heart block; Leads II and III complete A-V dissociation with bigeminy due to ventricular extrasystoles.

lower third of both lungs posteriorly and over these areas, moist râles were heard. The outermost point of cardiac action was seen and felt in the sixth left intercostal space in the mid-axillary line as a systolic heave of marked amplitude. The right cardiac border was percussed five centimeters from the midsternal line in the fifth interspace. There was a moderately loud systolic and blowing diastolic murmur best heard at the base but transmitted over the entire precordium. The pulmonic second sound was accentuated. During apnea, the rate was approximately 40 per minute and during hyperpnea, 78 per minute. The peripheral vessels were moderately thickened and Corrigan pulse, capillary pulsations and Duroziez's sign were present. The blood pressure was 154 mm. Hg systolic and 60 mm. diastolic during both apnea and hyperpnea in both arms. A firm liver edge was palpable two fingers'-breadth below the right costal margin. There was pitting edema over the ankles and the knee jerks and ankle jerks were absent.

Roentgenograms of the chest revealed the cardiac silhouette increased in all diameters especially in the region of the left ventricle. There was an increase in the supracardiac dullness particularly in the region of the ascending portion of the aorta, consistent with the diagnosis of specific aortitis or aneurysm of the aorta. The findings in the lungs were due to congestive changes.

The red blood count was 4,450,000 per cubic millimeter with a hemoglobin of 92 per cent. The white blood count was 8100 per cubic millimeter with normal differential. The fasting blood urea was 15 mg. per cent. The Wassermann and Kahn reactions were positive on three occasions. Repeated urinalyses revealed only an occasional slight trace of albumin.

An electrocardiogram, taken shortly after entry (figure 1*C*), revealed a partial (2:1) heart block in Leads I and IV and in Leads II and III a complete auriculo-ventricular dissociation with bigeminy due to alternate ventricular extrasystoles. The

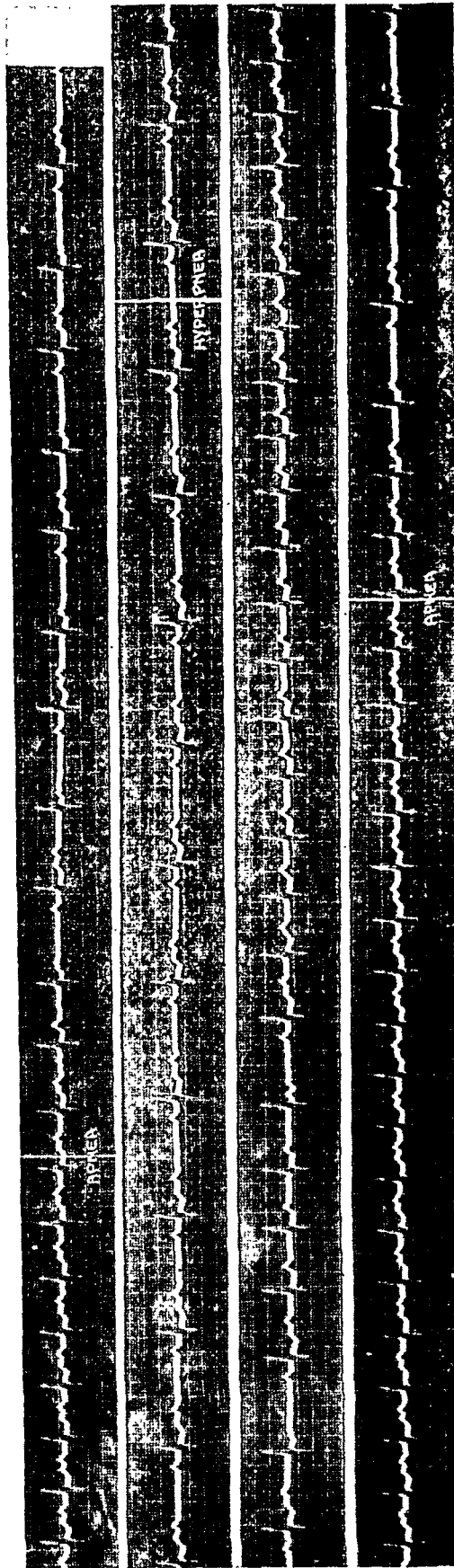


FIG. 2. Electrocardiogram, Lead II. Continuous tracing through a complete cycle of Cheyne-Stokes respiration showing transitions to and from partial (2:1) heart block.

Q-R-S complexes were slurred and showed left axis deviation. In Leads I and II the S-T segments were depressed and the T-waves diphasic. In the precordial lead, the T-wave was still inverted.

The diagnosis was syphilitic heart disease, cardiac hypertrophy and dilatation, aneurysm of the ascending aorta, aortic insufficiency, transient heart block, class III.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Numerous clinical and electrocardiographic observations under varying circumstances were made on this patient and the effect of various drugs was noted. All electrocardiographic studies were made on Lead II and control records were taken usually a half-hour before studies with different drugs or procedures. Only the more pertinent observations are presented.

Figure 2 (obtained after two days of hospitalization) is fairly representative of numerous control tracings and shows a continuous record taken during a complete cycle of Cheyne-Stokes respiration. The onset of apnea and hyperpnea was accurately recorded. At the end of the hyperpneic phase, the record shows a delayed auriculoventricular conduction (P-R equal to 0.30 second), depressed S-T segment, inverted T-wave and a ventricular rate of 83 per minute. With the onset of apnea, there occurs a rapid increase in the P-R intervals from 0.30 to 0.56 second following which 2:1 partial heart block appears. In the early stages of apnea, the rhythm alternates between a 2:1 heart block and a partial heart block with a prolonged P-R interval of 0.56 second; in the later stages there is a persistent 2:1 heart block. The ventricular rate decreased from 83 to 37 per minute and of particular interest are the further depression of the S-T segments and the greater inversion of the T-waves toward the end of apnea. During hyperpnea, progressive changes in the opposite direction take place. The ventricular rate increases, the degree of auriculoventricular conduction disturbance decreases, and the S-T segments and T-waves become slightly more elevated.

In reviewing the control tracings, it was found that in general, with the onset of apnea, the P-R interval increased until a 2:1 heart block appeared. On one occasion, complete auriculoventricular dissociation developed at the end of a prolonged period of apnea. The degree of auriculoventricular block always decreased with the restoration of breathing. There was a marked variation in the interval between the onset of apnea and the development of the abnormal rhythm. This was later correlated with the effects of digitalis. With rapidly increasing doses to the point of toxicity, the abnormal rhythm began to appear earlier in the apneic phase. Resnik and Lathrop³ attribute this to the increase of vagal tone by digitalis.

Studies by Anthony, Cohn and Steele⁴ on changes in the blood gases during Cheyne-Stokes respiration indicate that the lowest concentration of oxygen occurs at the beginning of the respiratory phase. The changes in the T-waves and in the S-T segments in our case were progressive in character and the maximum deviations were observed when the oxygen content was at its lowest level. These findings are consistent with the electrocardiographic changes found in experimentally induced generalized anoxemia.^{5, 6}

THE EFFECT OF VARIOUS THERAPEUTIC MEASURES

1. *Atropine.* It has been adequately demonstrated by Greene and Gilbert⁷ that the conduction disturbance in these cases is due to a central stimulation of

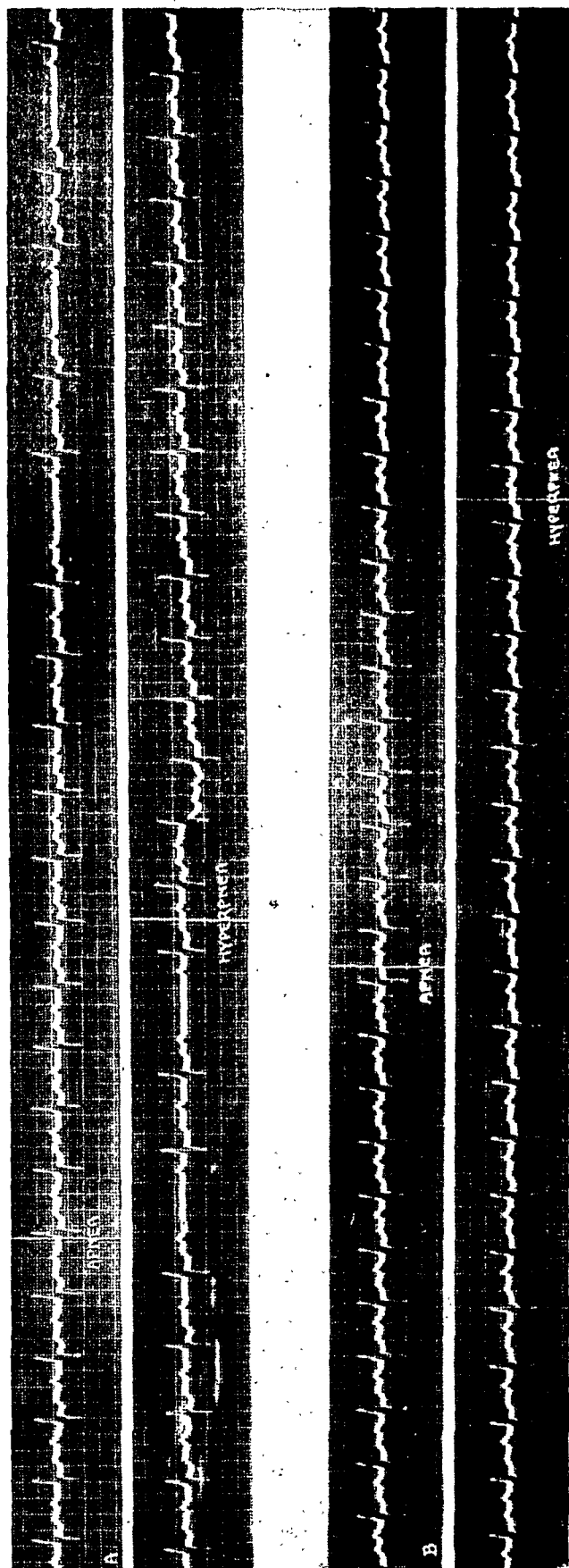


FIG. 3 *A.* Electrocardiogram, Lead II. Continuous tracing showing changes in rhythm during the apneic phase. *B.* Strip taken two minutes following intravenous injection of 1/50 grain of atropine sulphate.

the vagus nerves by anoxemia. Atropine was administered intravenously on four occasions in doses varying from 1/30 to 1/75 of a grain and tracings were obtained at intervals of 2, 5, 15, 30 and 60 minutes. On each occasion, atropine completely abolished the cyclic changes in cardiac rhythm without affecting the Cheyne-Stokes respiration.

Figure 3A is a continuous strip of Lead II beginning at the end of a hyperpneic phase of Cheyne-Stokes respiration and extending through the entire apneic phase into the succeeding period of hyperpnea. The ventricular rate during the respiratory phase is 81 per minute and the P-R interval 0.28 to 0.30 second. During apnea there is a gradual lengthening of the P-R interval and the development of 2:1 heart block. Figure 3B is a strip taken two minutes after the intravenous administration of 1/50 of a grain of atropine showing persistent Cheyne-Stokes respiration without transient heart block. The ventricular rate is 86 per minute and the P-R interval 0.24 second.

2. *Theophylline-Ethylenediamine*. Vogl,⁸ in 1927, first introduced euphyllin as a means of abolishing Cheyne-Stokes respiration and relieving the associated subjective distress, and summarized his experience five years later by stating that the drug never failed to bring about a normal type of respiration. Several investigators have confirmed these observations and have been almost as enthusiastic in their claims⁹⁻¹² although at the present time neither the effective component nor the exact mode of action of the drug is clear. Aminophyllin was administered intravenously in doses of 0.48 gram dissolved in 10 c.c. of saline on three occasions. In this patient, the injection abolished the apneic periods but periodic waxing and waning of respiration still persisted and during the latter, partial heart block still appeared. On one occasion, the additional injection of 0.24 gram failed to restore the respiratory rhythm to normal. The effect on respiration never lasted more than a half-hour and the patient was unaware of any subjective improvement.

3. *Caffeine Sodio-Benzoyate*. Experimentally, the effects of caffeine are complex and depend on the dosage and the conditions under which it is used. Its principal effect appears to be vasodilatation combined with stimulation sufficient to maintain and at times elevate the blood pressure.¹³ It has been demonstrated that caffeine produces a definite cerebral vasodilatation.¹⁴ Clinically, it has been stated that "caffeine—rarely, if ever, restores normal breathing."¹⁰ In our case caffeine sodio-benzoate was administered intravenously on three occasions in doses of 15 grains and tracings were obtained at five minute intervals for a half-hour. On each occasion, caffeine abolished both the Cheyne-Stokes respiration and the periodic heart block.

Figure 4A shows part of a record taken during apnea with partial heart block and a ventricular rate of approximately 45 per minute. Figure 4B is part of a tracing taken 10 minutes after the intravenous injection of 15 grains of caffeine sodio-benzoate. The ventricular rate is 83 per minute and the P-R interval 0.26 second.

4. *Morphine*. Cheyne-Stokes respiration has been produced experimentally by the administration of morphine. Electrocardiograms in these cases showed central vagal stimulation with sino-auricular and auriculoventricular block which could be abolished by atropine. Clinically, it has long been appreciated that patients with cardiac decompensation are quite often thrown into Cheyne-Stokes respiration by morphine.

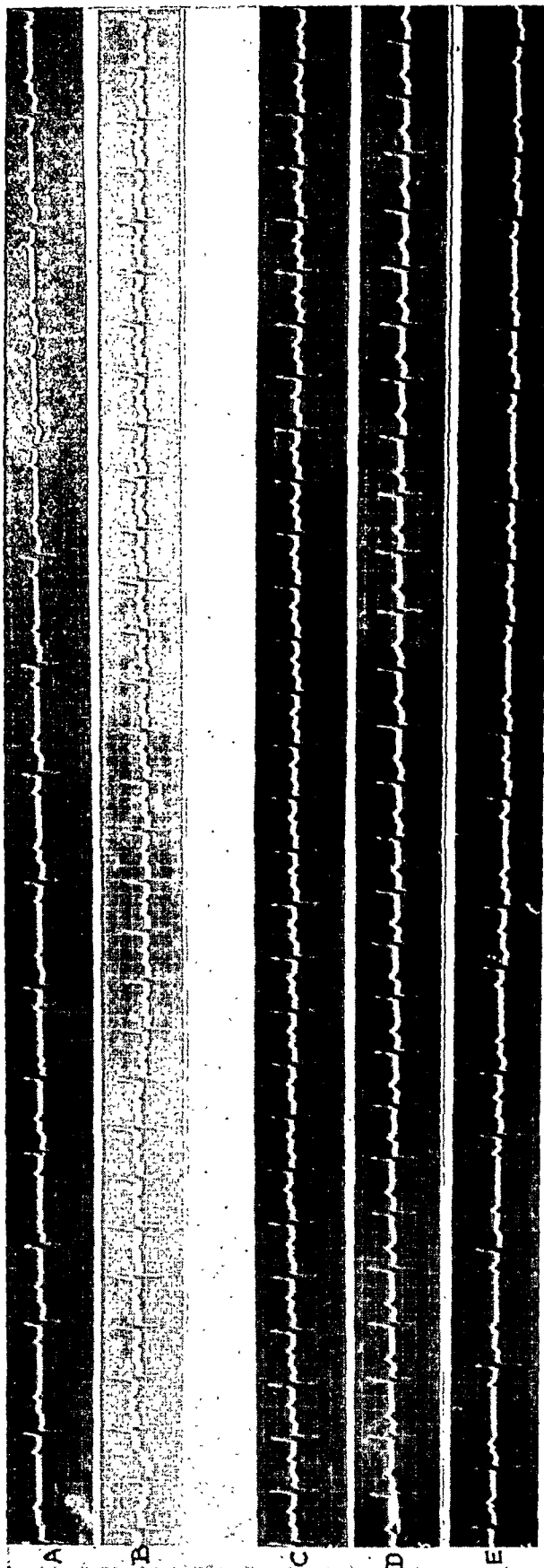


FIG. 4 *A.* Electrocardiogram, Lead II. Control strip taken during portion of apneic phase. *B.* Strip taken 10 minutes following intravenous injection of 15 grains of caffeine sodio-benzoate. *C.* Control strip taken during normal respiration. Rate 80 per min., P-R interval 0.28 sec. *D.* Tracing taken during apneic phase one hour after administration of 1/4 gram of morphine sulphate. Rate 77 per min., P-R interval 0.44 sec. *E.* Tracing taken during apneic phase one hour after the preceding record.

Following admission to the hospital, the patient had received 1/4 grain morphine at bedtime to allay restlessness and alleviate his dyspnea. On May 12, the morphine was discontinued and the next day clinical examination revealed normal respiration which persisted until May 16 when Cheyne-Stokes respiration reappeared. It was found that the patient had received 1/4 grain of morphine the night before for dyspnea. On May 17, a tracing was obtained during normal respiration and 1/4 grain of morphine was administered subcutaneously. Tracings were taken at half-hour intervals. Figure 4C shows part of the control tracing taken before morphine was given. The ventricular rate was 80 per minute and the conduction time 0.28 second. An hour later, Cheyne-Stokes respiration was present and figure 4D was taken during the apneic phase. The ventricular rate was 77 per minute and the P-R interval was 0.44 second. Two hours later the tracings revealed periodic heart block during the apneic phases of Cheyne-Stokes respiration (figure 4E). The experiment was repeated on May 18 with almost identical results.

5. *Acetyl-Beta-Methylcholine Chloride (Mechoyl)*. Because of its parasympathomimetic effects and the fact that it occasionally produces various degrees of heart block, mecholyl was given subcutaneously dissolved in water, in doses of 25 mg. on three occasions and 50 mg. on one occasion. Although the patient showed the usual systemic effects of the drug, it failed to influence the P-R interval or produce any degree of auriculoventricular block. The 50 mg. dose did, however, produce numerous ventricular extrasystoles from a single focus which were readily abolished by 1/50 grain of atropine intravenously.

6. *Digitalis*. In view of the characteristic effect of digitalis on the vagus nerves and the frequency with which it has been associated in the reported cases of transient arrhythmias associated with Cheyne-Stokes respiration¹ the patient was given 4½ grains of digitalis by mouth daily starting May 22. On May 29, after he had received 31½ grains and was complaining of nausea, clinical and electrocardiographic studies again revealed Cheyne-Stokes respiration with periodic heart block during apnea.

The effect of the following drugs was studied because of their supposed circulatory and respiratory actions:

Strychnine sulphate gr. 1/60 subcutaneously.

Epinephrine hydrochloride ½ and 1 c.c. of 1:1,000 dilution subcutaneously.

Glucose (50 per cent), 50 and 100 c.c. intravenously.

Nitroglycerine gr. 1/100 sublingually.

Paredrine hydrobromide* orally in doses of 60, 80 and 100 mg.

None of these drugs produced any appreciable effect on the Cheyne-Stokes respiration or the associated arrhythmia.

THE EFFECT OF CAROTID SINUS STIMULATION

The predominant effect obtained on numerous trials was slowing of the ventricular rate as a result of depression of both the sino-auricular and auriculo-ventricular nodes. Figure 5 is a continuous strip of Lead II showing the effect

* The paredrine hydrobromide was supplied by Smith, Kline and French Laboratories of Philadelphia.

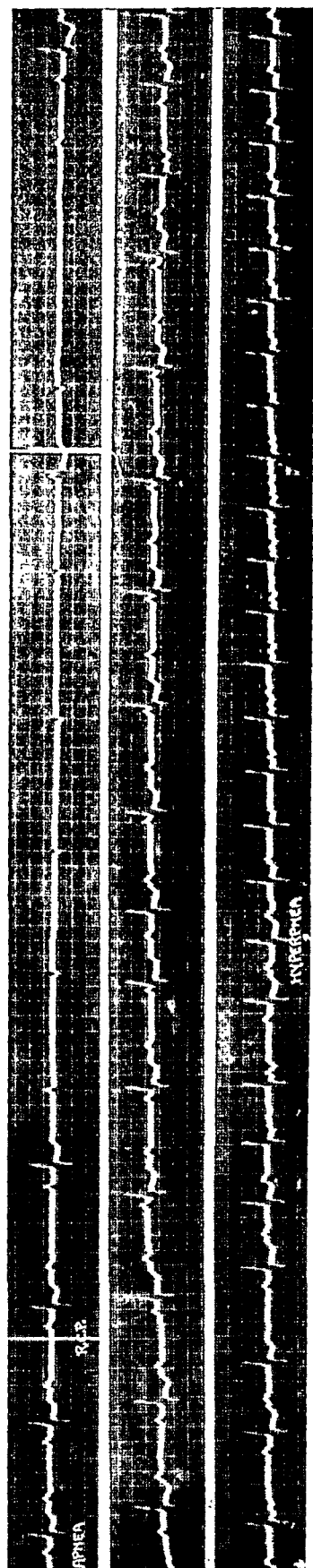


FIG. 5. Electrocardiogram, Lead II. Continuous tracing showing effect of pressure on the right carotid sinus (R.C.P.).

of right carotid sinus pressure applied during a period of apnea. Sinus slowing, ventricular and sino-auricular standstill, marked variation in size and shape of the auricular complexes and complete auriculoventricular block are present. During ventricular standstill, ventricular escape from an ectopic focus occurred. These changes were somewhat more pronounced on right than on left carotid sinus pressure. Repeated observations on the effect of carotid sinus stimulation during digitalization revealed a progressive sensitizing action on the vagal reflex. A rather interesting finding was the prolonged period of apnea which developed upon the return of ventricular activity. The duration varied from 40 to 60 seconds. Whether this was due to the sudden elevation of pressure in the carotid sinus and the abrupt return of blood flow through the respiratory center or to the return to the respiratory center of blood which had been over-oxygenated in the pulmonary vessels during the period of asystole is uncertain.¹⁵

EFFECT OF OXYGEN

There is sufficient evidence to support the theory that oxygen deficiency may play an important rôle in the production of Cheyne-Stokes respiration. Clinically, observers have obtained marked variation in the response to oxygen therapy, a result which may be correlated with the variation in oxygen saturation of the blood in different patients with periodic breathing. On two trials, 50 per cent oxygen administered via the open Burgess box¹⁶ quieted the patient's breathing and resulted in subjective improvement without influencing the periodic changes in cardiac rhythm. Oxygen administration did not abolish the periodic breathing even when the oxygen content was raised to a level of 95 per cent for a period of six hours.

DISCUSSION

This case afforded an unusual opportunity to study the factors influencing the occurrence and disappearance of heart block associated with Cheyne-Stokes respiration. The observations that digitalis, morphine and carotid sinus pressure, which are known to increase vagal tone, either induced or accentuated the heart block while atropine abolished the block, confirmed the vagal origin of the periodic variations in rhythm. The failure of epinephrine, 50 per cent glucose and paredrine to modify the block supports the view that the vagus is the mechanism by which the block was produced.

Contrary to usual experience, caffeine sodio-benzoate was the only measure which restored normal breathing and coincidentally abolished the transient heart block in this patient. Whether this was due to stimulation of the respiratory center is problematical. Oxygen administration resulted in subjective improvement without affecting the periodic respiration while aminophyllin, except for a slight modification of the type of respiration, was ineffectual. The failure of mecholyl to reproduce the heart block was attributed to the individual variation in response to the drug.

SUMMARY

A case is reported showing transient A-V block during the apneic phase of Cheyne-Stokes respiration. The effect of various drugs and procedures on the heart block is discussed.

BIBLIOGRAPHY

1. STEELE, J. M., and ANTHONY, A. J.: Arrhythmia of the heart associated with Cheyne-Stokes breathing. Report of a case showing auriculo-ventricular block, *Am. Heart Jr.*, 1933, viii, 357.
2. (a) BULLRICH, R. A., and MOIA, B.: Bloqueo cardiaco periódico en el ritmo de Cheyne Stokes, *Rev. argent. de cardiol.*, 1934, i, 145.
 (b) HILL, G. W., and MACKINNON, A. U.: The association of Adams-Stokes attacks with Cheyne-Stokes respiration: With a case report, *Edinburgh Med. Jr.*, 1934, xli, 513.
 (c) FLANDIN, C., POUMEAU-DELILLE, G., and ISRAEL: Tachycardie ventriculaire periodique au cours du rythme de Cheyne-Stokes, *Paris méd.*, 1937, i, 137.
 (d) KLEIN, F., and MULDER, J.: Ademhaling van Cheyne-Stokes, Hartblock en aanvallen van Adams-Stokes, *Nederl. tijdschr. v. geneesk.*, 1938, lxxxii, 3832.
 (e) VAN NIEUWENHUIZEN, C. L. C.: Periodes van Luciani als corzaak van aanvallen van Stokes-Adams, het verband tusschen Cheyne-Stokes' ademhaling en Stokes-Adams aanvallen, *Nederl. tijdschr. v. geneesk.*, 1938, lxxxii, 2801.
 (f) COMEAU, W. J.: Cheyne-Stokes respiration and auriculoventricular conduction, *New England Jr. Med.*, 1938, ccxix, 977.
3. RESNIK, W. H., and LATHROP, F. W.: Changes in the heart rhythm associated with Cheyne-Stokes respiration, *Arch. Int. Med.*, 1925, xxxvi, 229.
4. ANTHONY, A. J., COHN, A. E., and STEELE, J. M.: Studies on Cheyne-Stokes respiration, *Jr. Clin. Invest.*, 1932, xi, 1321.
5. ROTHSCHILD, M. A., and KISSIN, M.: Induced general anoxemia causing S-T deviation in the electrocardiogram, *Am. Heart Jr.*, 1933, viii, 745.
6. KATZ, L. N., HAMBURGER, W. W., and SCHUTZ, W. J.: The effect of generalized anoxemia on the electrocardiogram of normal subjects. Its bearing on the mechanism of attacks of angina pectoris, *Am. Heart Jr.*, 1934, ix, 771.
7. GREENE, C. W., and GILBERT, N. C.: Studies on the responses of the circulation to low oxygen tension. VI. The cause of the changes observed in the heart during extreme anoxemia, *Am. Jr. Physiol.*, 1922, ix, 155.
8. VOGL, A.: Erfahrungen über Euphyllin bei Cheyne-Stokes und andren Formen zentraler Atemstörung, *Med. Klin.*, 1932, xxviii, 9.
9. GRÜTER, R.: Ueber das Theophyllin-Aethylindiamin, *München. med. Wchnschr.*, 1936, lxxxiii, 1091.
10. GREENE, J. A., and HEEREN, R. H.: Observations on Cheyne Stokes respiration: The effect of drugs and mechanical measures which produce vasodilatation and vasoconstriction; *Med. Papers dedicated to Henry A. Christian*, 1936, p. 51, Waverly Press, Inc.
11. MARAIS, O. A. S., and McMICHAEL, J.: Theophylline-ethylenediamine in Cheyne-Stokes respiration, *Lancet*, 1937, ccxxxiii, 437.
12. NATHANSON, M. N., and FITZGIBBON, J. P.: Pharmacology of Cheyne-Stokes respiration, *Am. Heart Jr.*, 1939, xvii, 691.
13. SOLLMAN, T.: A manual of pharmacology, 5th Ed., 1937, W. B. Saunders Co., Philadelphia.
14. FINESINGER, J. E.: Cerebral circulation. XVIII. Effect of caffeine on cerebral vessels, *Arch. Neurol. and Psychiat.*, 1932, xxviii, 1290.
15. THOMAS, H. M., JR.: The effect of ventricular asystole on respiration, *Bull. Johns Hopkins Hosp.*, 1936, lix, 213.
16. BURGESS, A. M., BRIGGS, A. S., and BURGESS, A. M., JR.: Oxygen therapy by the open box method, *New England Jr. Med.*, 1934, ccx, 254.

IDIOPATHIC APLASTIC ANEMIA WITH RECOVERY*

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It is well known that recovery from "idiopathic" aplastic anemia is extremely unusual. Wintrobe¹ was able to find only six cases in his review of the literature. We report here a seventh cured case which we feel to be true idiopathic aplastic anemia.

CASE REPORT

A. T., a 30-year-old, married, white male, sugar refinery worker was admitted to the hospital on April 14, 1937. His presenting complaints were weakness and pallor for three months. The family history was negative. He had measles as a child, influenza in 1919, and a rather acute diarrhea for one week in 1927. He had been employed for the last three years as foreman in a sugar warehouse, exposed to dust but no chemicals. One year before the present illness the patient had boiled some crude coal tar in his cellar. All of the windows were tightly closed and he was exposed to the choking fumes for about one hour. There was no immediate ill effect from this nor are such fumes considered a cause of aplastic anemia. There was no history of exposure to roentgen-ray, radium, benzol, arsenobenzol, acetarsone, benzedrine, sulfanilamide, gold salts or any other drugs or industrial poisons. The patient's wife, child and fellow workers have remained well.

In January 1937, about three months before entry, the patient's associates commented on his pallor. Shortly after this he noted increasing fatigue, exertional dyspnea, palpitation and pounding in the ears. He continued to work but the symptoms progressed with added dizziness on rising, tingling of the fingers and on occasion a few crops of petechiae. His doctor diagnosed anemia which did not respond to parenteral liver injections so that he was sent to the hospital.

Physical examination on admission showed a vigorous, healthy looking, but very pale young man. Temperature 37.8° C. by rectum, pulse 118, respirations 22, and blood pressure 125 mm. of Hg systolic and 65 diastolic. There were recent hemorrhages and small plaques of grayish-white exudate along the vessels in both fundi and a few petechiae in the conjunctivae, and on the soft palate. The heart seemed a little enlarged. There was a loud systolic murmur. A normal liver edge was palpable about two fingers'-breadth below the costal margin. Spleen was not palpable. There was no other evidence of hemorrhage, no jaundice, or papillary atrophy of the tongue, and neurological examination was normal.

Examination of the blood showed: red blood cells 1.41 million; hemoglobin, 38 per cent (Sahli); white blood cells 3,800 with 30 per cent polymorphonuclears, 4 per cent of which were banded, and 70 per cent lymphocytes. Packed cell volume equaled 10.5 per cent. Hematocrit studies showed: M.C.V. 71; M.C.H. 40; M.C.H.C. 57. Bleeding time was over 10 minutes. There were 21,150 platelets per cubic millimeter and reticulocytes equaled 3.7 per cent of the red blood cells.

Urine, stool and blood Wassermann test were negative. Direct Van den Bergh test was negative and the indirect test showed 0.81 mg. %. Icterus index was 5.7 units. Gastric analysis, following histamine, yielded a maximum ten-minute volume of 47 c.c., free acid 86 degrees, and total acid 108 degrees. A petechiometer test showed spots to appear on the upper forearm in one minute at 20 mm. of Hg suction. A control was negative in this time at 40 mm. suction. Chest roentgenogram showed

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the lungs to be clear, but the left ventricle was somewhat enlarged. Roentgenograms of the bones revealed nothing unusual. A blood culture was negative. A sternal marrow biopsy was done on April 20 and the specimen was described by Dr. Wyckoff as follows: "The cellularity of the marrow is very considerably reduced. Some areas of the stroma contain but a few scattered hematopoietic cells. In other parts the stroma is reduced to narrow bands between large fat cells. Megakaryocytes are few. No considerable erythropoietic foci are seen. Those found are small and imperfect. Fairly numerous endothelial phagocytes (histiocytes) are found. The cytoplasm of these cells contains pigment. Conclusion: Aplasia of the marrow."

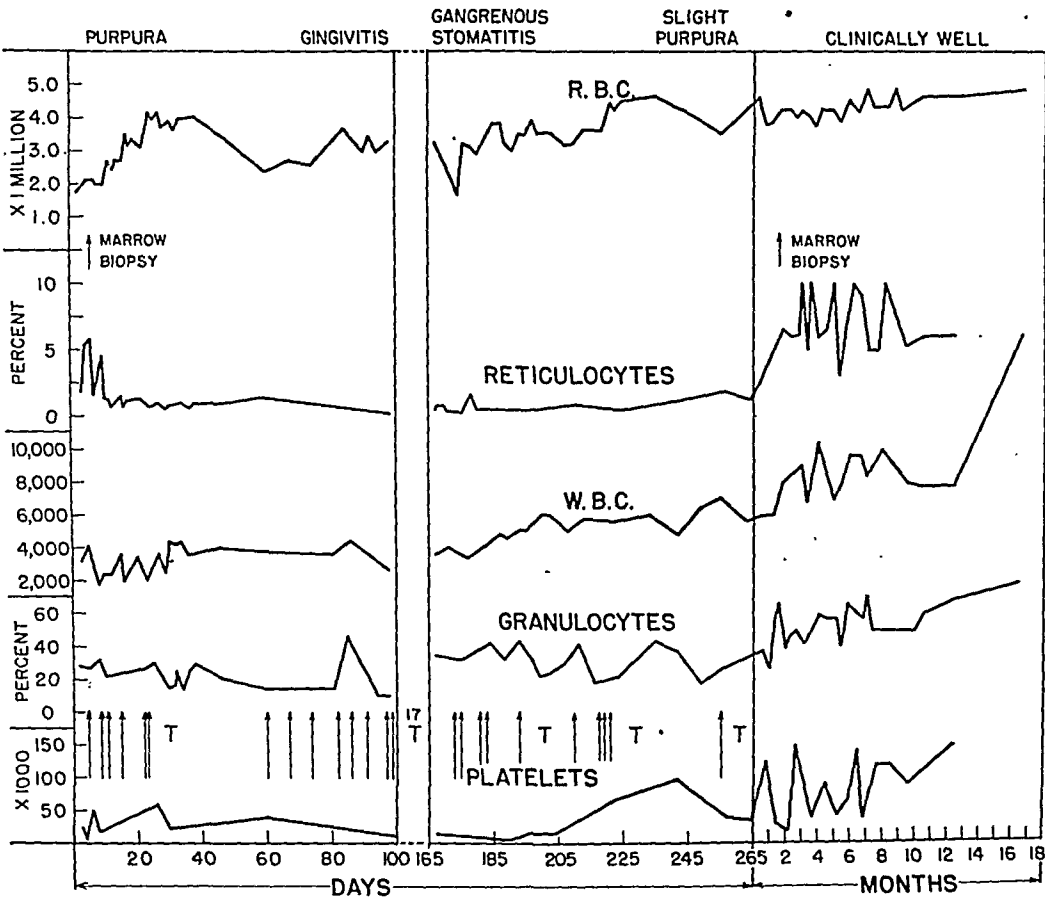


CHART 1. Hematological findings in patient A. T. (T represents transfusion.)

The patient was fortunate in having plenty of blood donors at his disposal. His treatment and course in the hospital are summarized in the accompanying chart which covers 25 months' observation. He received 41 blood transfusions in the first nine months, totaling about 20 liters of citrated blood. Other treatment consisted of bed rest and nursing care, high vitamin diet, ferrous sulfate 1.2 gm. daily, 100 gm. of raw liver daily for the first three months, and brewers' yeast 3 gm. daily during convalescence. His course was exceedingly stormy for eight months after admission. Purpura, prolonged bleeding time, anemia, and neutropenia persisted despite transfusions. There was an initial fever which fell to near normal in the first six weeks of observation. During the fourth month he developed a severe gingivitis with loosening of all the teeth, much pain, high fever, general toxicity, swollen tongue and edema of

the face. There gradually developed an immense gangrenous lesion involving the gums and soft palate near the right back teeth. This had the characteristic foul odor of a gangrenous naso-pharyngitis and smears showed Vincent's organisms. For a time the patient seemed desperately ill.

During October and November 1937 a change for the better took place. The blood returned toward normal, with a rise in erythrocytes, hemoglobin, total white count, percentage of granulocytes and platelets. Interestingly, there was no reticulocytosis until later. The hematological improvement was mirrored in the clinical condition, the temperature falling to normal, rapid healing of the gangrenous mouth lesions, disappearance of purpura and gain in strength.

A second sternal biopsy in February 1938 showed that: "The stroma of the marrow is moderately cellular in distinct contrast to the all but aplastic marrow obtained from the sternum on April 20, 1937. In some areas of the section fairly well defined foci of active red cell formation are found. The surrounding stroma contains leukogenic cells in moderately active multiplication. An occasional megakaryocyte is found."

The patient's convalescence was smooth and sustained. He returned to his work apparently cured in September 1938, 18 months after his first entry and 21 months after the onset of his disease. Our last blood count showed: red blood cells 4.85 M., hemoglobin 98 per cent; white blood cells 17,500, with polymorphonuclear neutrophils 73 per cent (banded 6 per cent, segmented 67 per cent), eosinophiles 4 per cent, basophiles 1 per cent, lymphocytes 15 per cent, monocytes 7 per cent and reticulocytes 9 per cent.

Wintrobe comments upon the fact that in all of the six other reported patients with idiopathic aplastic anemia who have lived for over one year some abnormality of the blood has persisted. There has been either moderate anemia, leukopenia, thrombopenia or combinations of them. In our patient a reticulocyte count of between 5 and 10 per cent persisted for one year. There has been no subsequent purpura but the platelets have never returned entirely to normal levels, ranging between 50 and 150 thousand per cubic millimeter. The red cells were still macrocytic and hyperchromic one year after the first observation.

REFERENCE

1. WINTROBE, M. M., STOWELL, A., and ROLL, R. M.: Report of a case of aplastic anemia following gold injections in which recovery occurred, *Am. Jr. Med. Sci.*, 1939, cxcvii, 698.

TOTAL THYROIDECTOMY FOR CONGESTIVE HEART FAILURE AND ANGINA PECTORIS; REPORT OF A CASE *

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CHRISTIAN¹ stated in 1925 that possibly a lowered metabolic rate as a result of thyroid deficiency might afford a cardiac rest in that it lessened appreciably the demands on the heart. He also made the observation that those suffering from myxedema often developed symptoms of angina pectoris upon administration of thyroid, with subsequent improvement upon withdrawal of the thyroid.

In 1927 Levine² did a subtotal thyroidectomy for masked hyperthyroidism

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on a patient in cardiac failure. Great improvement followed but upon careful microscopic examination of the removed gland no areas of hyperactivity of the gland could be found.

Upon the basis of previous exhaustive work by Blumgart and his associates on the blood velocity in its relation to metabolic activity Blumgart³ states that the "adequacy of a given velocity of blood flow cannot be decided in absolute terms. It can only be evaluated in relation to the metabolic demands of the particular patient." The basal metabolism in cardiac failure is normal, yet the blood velocity is slow. In those suffering with myxedema the metabolic rate is low and the blood velocity is also retarded. Hence it follows that if the metabolic rate could be lowered sufficiently to enable the slowed blood velocity to take care of the demands put upon it the cardiac failure would be greatly relieved.

The first such operation was done at the Peter Bent Brigham Hospital in Boston in 1932. Since that time the procedure has been critically reviewed and is now used with increasingly more careful judgment. In fact there is much criticism of the entire rationale in some quarters, and in a few it has been discarded. The consensus of opinion at the present time favors the operation for angina pectoris but feels that it is questionable in congestive failure. Parsons and Purks⁴ in a paper in which they quote personal communications from various men state that Mont Reid, Moore and Trout do not feel that the procedure is justified, and that Clute is not convinced of its efficacy, while Pemberton feels that it is sound from a physiological standpoint and Brenzer is in favor of it.

One of the greatest problems is the selection of the proper cases. It is felt by all that the operation is too radical for any case that has not been carefully tried first on all proved medical therapy and has not responded satisfactorily. It is then and only then that one is justified in proceeding with the measure. In congestive failure the operation should not be performed on those with any active cardiac lesion or rapidly progressing failure. Active rheumatic heart disease and even latent luetic heart disease are definite contraindications. Advanced cirrhosis of the liver is obviously a contraindication. Renal function must be adequate without evidence of abnormal nitrogen retention.

In the selection of cases of angina pectoris the considerations in addition to the above must deal with the economic problem. Only if the pain occurs when the patient is at rest or when it interferes with his only means of livelihood should he be considered seriously. If there has been a recent coronary occlusion the operation is certainly not indicated.

The preoperative basal metabolic rate is of great significance. One below minus 15 per cent offers less chance for relief than one higher, and operation is not advisedly offered when the basal metabolism is minus 20 per cent or lower. Other instances present difficulties in determining whether slightly elevated rates are due to a masked hyperthyroidism or occur with a normal thyroid gland. Levine and Eppinger⁵ cite an instance where the basal metabolic rate was as high as plus 45 per cent, yet careful pathologic section of the gland failed to reveal any evidence of overactivity.

After operation, as the extremely low basal metabolic rates develop and symptoms of myxedema sufficiently profound to cause discomfort ensue, small doses of thyroid are indicated. It is best to keep the basal metabolic level around minus 20 per cent. However, many of these patients, even those not so

afflicted prior to operation, are unable to tolerate thyroid medication without the appearance of angina pectoris symptoms. In such cases the thyroid is immediately withdrawn; in each case the administration of thyroid is entirely an individual problem.

Levine and Eppinger⁵ find that with the lowering of the basal metabolic rate the blood velocity (sodium dehydrocholate method) either remains the same or increases. While theoretically this does not seem altogether logical it is found to be clinically true. Hence the improvement in the cardiac state.

Significantly, the blood cholesterol has been found to rise proportionately with the reduction in basal metabolic rate. There is often a high preoperative blood cholesterol level, the cause of which is not understood.

Stern and Altschule⁶ point out that as the basal metabolic rate falls to minus 20 or 30 per cent a slight secondary anemia develops, of a macrocytic, hyperchromic type. In those in whom there is some degree of emphysema the anemia is not so great. In no case is the anemia so great as to cause any symptoms. The cause of the anemia is not established, although it is probably due to a decreased function of the bone marrow. The anemia does not respond to either liver or iron, but upon administration of thyroid shows improvement. There is also a lowering of the total white count which, however, responds normally to infection.

The effect of the procedure on blood pressure is not significant. While immediately following the operation there may possibly be a slight drop in pressure this may be due to the bed rest imposed by the procedure. Some time after the operation Levine and Eppinger⁵ found the pressures possibly a little elevated over the preoperative level but not to a clinically significant extent.

The heart size has been found to increase gradually but whether this is due to the myxedema or to the gradual progression of the cardiac lesion is a problem for conjecture. It is certainly true that the myxedematous heart does enlarge gradually but whether either factor alone is responsible is a question that is not clear. Claiborne and Hurxthal⁷ in their series of cases made note of the fact that there was no increase in heart size following the onset of the myxedema.

It is felt by many that the relief from pain in angina pectoris is due to the interruption of the sensory nerves of the heart rather than to the thyroidectomy itself. It is certain that the immediate dramatic relief of pain could not be due to the physiological results of the thyroidectomy, for the basal metabolic rate does not reach its effective level prior to two or three weeks after the operation. Weinstein and Hoff⁸ point out that the superior and middle cardiac nerves of the sympathetic system and the superior rami of the vagus nerves are in close contact with the posterior capsule of the thyroid gland and contribute to the nerve supply of the thyroid gland. Moreover, they found that when only one lobe was removed relief from pain was obtained only on that side. Dissections in this region disclosed that the superior cardiac nerve lies in close apposition to the posterior capsule in 70 per cent of the cases and the middle cardiac nerves in 20 per cent of the cases. These authors concluded that the early relief of pain was due to the interruption of these nerves rather than to the reduction of thyroxine in the circulation.

Ochsner and Gillespie,⁹ while recognizing the interruption of the sensory nerves as a factor in the relief of the pain in angina pectoris, also feel that the

smaller amount of work demanded of the heart, the decreased sensitivity to adrenalin, and the generalized decreased vasomotor tone are equally if not more important factors.

The present general feeling is that the procedure is justified in intractable cases of angina pectoris but is of doubtful value in congestive heart failure. Parsons and Purks⁴ report a series of 392 cases gathered from 59 different sources (personal communications and reported in the literature). Of these, 229 were done for congestive failure with an operative mortality of 10.48 per cent. Of the remaining cases 34.63 per cent showed excellent results, 28.78 per cent moderate improvement, 2.92 per cent slight improvement and 33.63 per cent failures or no improvement. In the series of cases done for angina pectoris there was an operative mortality of 3.75 per cent, with the remaining cases showing excellent results in 55.46 per cent, moderate improvement in 28.12 per cent, slight improvement in 3.92 per cent and unsatisfactory results in 12.5 per cent. Weeks,¹⁰ in a series of 100 cases of angina pectoris, reports an immediate operative mortality of 3 per cent with a later mortality of 15 per cent not related to the operation itself. Of the remaining cases 51.2 per cent were markedly improved, 40.2 per cent moderately improved and 8.5 per cent failures. McCreery¹¹ reported a series of 150 cases done for congestive failure, with an immediate operative mortality of 9.3 per cent, late but not operative deaths of 16 per cent, markedly improved 41.9 per cent, moderately improved 39.2 per cent, and no improvement 18.7 per cent. Hence it is readily seen in each series that the results were definitely better in those cases suffering from angina pectoris. On the other hand, worthwhile results were obtained in those with congestive failure; and when one is faced with the fact that medical therapy has been pushed to the utmost in all cases subjected to this heroic procedure it should not be discarded as useless in congestive heart failure.

The postoperative complications of tetany and injury to the recurrent laryngeal nerves are relatively infrequent. No doubt as the procedure becomes more common the incidence of such complications will become even less. Parsons and Purks⁴ state that in the series they collected there was transient tetany in 10.3 per cent with only one fatality, and injury to the recurrent laryngeal nerve in 8.2 per cent which also was transient and offered no difficulties.

Cohen and Hermann¹² in making a social study on a group of 47 cases that had survived the operation at least one year found that 40 of these patients had experienced definite improvement and lived with greater ease and activity. Twenty-three of the group had been able to resume remunerative work or to take up complete housework for a period of three months to two and a half years. They report that half of the congestive failure cases and a slightly smaller percentage of the angina cases presented the best results. It is finally concluded from this study that the procedure, on the whole, is a definite economic aid and is entirely worthwhile from a social and economic standpoint.

CASE REPORT

E. J., a 51-year-old white female, was first seen at St. Luke's Hospital, St. Louis, Missouri, in January 1932, suffering from cholecystitis with jaundice. At the time of admission she gave a history of scarlet fever in childhood. In the weeks prior to admission she had suffered from dyspnea, occasional orthopnea, and edema of the ankles. Upon examination a rough systolic murmur was heard over the mitral area,

with an accompanying apical thrill, blood pressure 90 mm. Hg systolic and 78 mm. diastolic. In addition she was jaundiced; the liver was found to be about two to three fingers'-breadth below the right costal margin; and there was tenderness in the right upper quadrant. A cholecystectomy and appendectomy were performed in February 1932, at which time gall-stones were found. Postoperatively pleurisy developed on the left side and a stormy course ensued. An electrocardiogram at the time was normal. In April 1932 she definitely decompensated but responded readily to digitalization. The electrocardiogram was again normal, and the rate regular, but the blood pressure hovered around 140 mm. Hg systolic, and 85 mm. diastolic. In August of 1932 precordial pain was first noticed following exertion. In October of the same year a subtotal hysterectomy was done because of fibromyomata, with a right sided pneumonia developing 10 days after operation. From this she recovered without cardiac decompensation. The heart remained regular, and the basal metabolism was plus 12 per cent. At this time the notation was made that the pulse remained in the region of 100 per minute even though digitalis was pushed to toxicity. In March 1933 she appeared in the clinic with threatening decompensation, and was hospitalized in April with disabling decompensation. It was at that time that fibrillation was first noticed and that the electrocardiogram showed signs of myocardial injury. The blood pressure was found to vary between 120-140 mm. Hg systolic and 70-90 mm. diastolic. Following a month in the hospital, where she was treated symptomatically and by bed rest, she was discharged. During the next four to five months she presented herself at the clinic frequently with complaints of dyspnea, edema, orthopnea, and signs of myocardial failure. On September 2, 1933 she was admitted to the hospital with a large pleural effusion on the right which necessitated draining on September 2, October 9, and October 24, about 20 ounces of fluid being removed each time. The blood pressure had risen to 165-190 mm. Hg systolic and about 110 mm. diastolic, at which levels it maintained itself during her hospital stay. From then until January 1934 she was admitted to the hospital at increasingly shorter intervals for thoracentesis until it was finally necessary to keep her in the hospital constantly because she was unable to go back and forth to her home.

At the time operation was contemplated her vital capacity was found to be about 2400 c.c. The blood velocity by the intravenous Decholin method was 30-39 seconds. The blood N.P.N. was 28 mg. per cent. The patient was orthopneic, but upon complete bed rest the edema disappeared, the fluid disappeared from the right chest, and the patient was considerably more comfortable. The heart continued to fibrillate at a moderately rapid rate; the heart sounds remained unchanged; and the electrocardiogram showed myocardial damage. Basal metabolism before operation was plus 10 per cent and plus 0.5 per cent on two different occasions. The blood pressure was 160 mm. Hg systolic and 90 mm. diastolic. Total thyroidectomy was done February 9, 1934 without complication except for slight injury to the recurrent laryngeal nerve. Within two weeks the patient was able to sleep flat in bed, the pulse had slowed to 72 but was still fibrillating, and while there was a friction rub at the right base there was no fluid. There was no elevation of temperature following the procedure. The blood velocity was 32 and 33 seconds by the Decholin method on two occasions. The basal metabolic rates were as follows:

Feb. 21, 1934	Minus	1	per cent	
March 1, 1934	"	8	"	"
March 9, 1934	"	13	"	"
March 19, 1934	"	15	"	"
April 6, 1934	"	22½	"	" Discharged from hospital

The thyroid gland was found to be entirely normal on pathological section. Digitalis was omitted, and the pulse remained in the seventies although fibrillation con-

tinued without interruption. The blood pressure was around 150–160 mm. Hg systolic and 90–100 mm. diastolic. However, in May of 1934 she was digitalized again and was more comfortable. In June 1934 the basal metabolism was found to be minus 6 and minus 3 per cent on two occasions; hence, roentgen-ray therapy was given for any thyroid tissue that might have been overlooked inadvertently. In August of 1934 the basal metabolic rate was minus 8 per cent. However, she felt definitely improved, was able to take care of all her housework except the heavy mopping and sweeping, and slept flat in bed. Occasionally she had some edema of the ankles but never a great deal, and at no time did she have pleural effusion. She did have dyspnea on exertion and was never able to walk long distances.

In December of 1934 the blood pressure reached 190 mm. Hg systolic and 100 mm. diastolic, at which approximate levels it remained until death. She was unable to tolerate thyroid in any considerable dosage without the occurrence of anginal pains.

Through 1935 she was very comfortable, being able to work around the house and do about as she desired. However, she was never able to be without digitalis. She also insisted upon having the so-called coronary dilators. If these were omitted and another tablet substituted in their place without her knowledge she would invariably call within the next day or so stating that she was having anginal symptoms and asking if the medicine had not been changed.

In 1936 she began to show her first signs of failure, more dyspnea upon exertion, slight orthopnea, and some precordial distress on slight exertion. In February of 1936 her basal metabolism was minus 7 per cent. In spite of these relatively normal readings she complained of feeling cold and always wore extra clothing in an effort to keep warm. Her skin and hair were dry and coarse. There was a mild secondary anemia and the blood cholesterol was found to be elevated, remaining in the region of 300 mg. per cent.

In 1937 and 1938 her course was gradually downhill. The basal metabolism was minus 30 per cent in January 1938. It was not until the spring of 1938 that she again developed pleural effusion which even then was not sufficient to necessitate thoracentesis and was later absorbed. In November of 1938 she was forced to enter the hospital in marked decompensation. During her stay there until April of 1939 she was never able to tolerate a basal metabolism. In January of 1939 she developed a right pleural effusion which never reached large proportions. She died May 20, 1939. At autopsy no evidence was found of the thyroid gland. The heart was enormously enlarged, and the valves revealed definite rheumatic involvement. There was a small pleural effusion on the right, and the liver and lungs showed the expected findings of congestive heart failure.

Critical review of the roentgen-rays of the chest for heart size during the years revealed that there was a slight additional enlargement of the heart just following the thyroidectomy, but from then until the time of death the heart remained approximately the same in size.

COMMENT

Total thyroidectomy for heart failure and angina pectoris is a valuable procedure as evidenced from the reports in the literature and this particular case. It has a sound physiological basis and the clinical results have been definitely favorable. While the statistics in the literature report better results in angina pectoris the results in congestive heart failure are encouraging and do offer relief to a large percentage of cases.

It is to be noted that the blood velocity, blood pressure and heart size are little changed by the procedure. Yet the demands made upon the heart are

definitely lessened by the reduction of the metabolic rate and hence aid the failing heart considerably.

This particular case calls attention to the observation made by Christian¹ that the use of thyroid in the myxedematous heart may bring on signs of angina pectoris. Also, in the discussion of the so-called coronary dilators this patient apparently gives clinical evidence of their value.

From the social and economic point of view the procedure deserves particular consideration. In this instance it was of vital importance that life be spared as long as possible in order that the patient might help raise her orphaned grandchildren. With an added five years of activity she was able to give much needed assistance. As pointed out by Cohen and Hermann¹² the social and economic significance of the measure is well worth serious consideration, and its use is often justified from that standpoint.

CONCLUSIONS

1. Total thyroidectomy for angina pectoris and congestive heart failure has a sound physiological basis.
2. While the procedure gives more favorable results in angina pectoris, the results in congestive failure justify the operation in that condition also.
3. A case is reported of total thyroidectomy for congestive heart failure in which excellent results were obtained.

BIBLIOGRAPHY

1. CHRISTIAN, HENRY A.: The heart and its management in myxedema, Rhode Island Med. Jr., 1925, viii, 109.
2. ROSENBLUM, H. H., and LEVINE, S. A.: What happens to patients with hyperthyroidism and significant heart disease following subtotal thyroidectomy? Am. Jr. Med. Sci., 1933, clxxxv, 219.
3. BLUMGART, H. L., LEVINE, S. A., and BERLIN, D. D.: Congestive heart failure and angina pectoris—the therapeutic effects of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity, Arch. Int. Med., 1933, li, 866.
4. PARSONS, W. H., and PURKS, W. K.: Total thyroidectomy for heart disease, Ann. Surg., 1937, cv, 722.
5. LEVINE, S. A., and EPPINGER, E. C.: Further experiences with total thyroidectomy in the treatment of intractable heart disease, Am. Heart Jr., 1935, x, 736.
6. STERN, B., and ALTSCHULE, M. D.: Hematological studies in hypothyroidism following total thyroidectomy, Jr. Clin. Invest., 1936, xv, 633.
7. CLAIBORNE, T. S., and HURXTHAL, L. M.: Results of total thyroidectomy in heart disease, New Eng. Jr. Med., 1937, ccxvi, 411.
8. WEINSTEIN, A. A., and HOFF, H. E.: Mechanism of the relief of pain immediately after total thyroidectomy for angina pectoris in congestive failure, Surg., Gynec. and Obst., 1937, lxiv, 165.
9. OCHSNER, A., and GILLESPIE, C.: Total thyroidectomy for cardiac disease, New Orleans Med. and Surg. Jr., 1936, lxxxviii, 422.
10. WEEKS, C.: Total thyroidectomy for relief of pain of angina pectoris, Surg. Clin. N. Am., 1936, xvi, 667.
11. MCCREERY, J. A.: Total thyroidectomy for congestive heart failure and angina pectoris, Ann. Surg., 1936, ciii, 136.
12. COHEN, E. and HERMANN, R. L.: Social study of patients with chronic cardiac disease treated by total thyroidectomy, New Eng. Jr. Med., 1936, ccxv, 1.

EDITORIAL

IN TIMES OF STRESS

THIS is a period in our history as a nation when the great winds of change are blowing and we must each play a part in seeing that it is the chaff only which is carried away and that we retain the sound truths by which our form of society lives. The physician especially should by his training and his experience be fitted to comprehend that there are values which are permanently a part of the human organism and that any plan for society which contravenes these built-in beliefs of the human race can succeed only for the brief duration of a period of mass hysteria. Destructive as a hysterical nation may be and great as may appear its successes, if its principles of action contradict the instinctive faiths of man it is doomed to ultimate failure.

Hysteria is, however, a contagious phenomenon. A mass negation by an afflicted nation of the slowly developed code of social and international morality, if it leads to striking immediate successes, has a great influence on the stability of other nations. The weaker ones in each people begin to be uncertain of their own beliefs and to question whether perhaps indeed the very world has changed and the old truths, such as honor, tolerance, mercy and the equal rights of the weak and the strong, been swept away. A nation which seriously questions its own beliefs is in danger of not standing firm.

Our knowledge of man, and of man's reactions is perhaps as wide and is certainly more solidly founded than that of any other group in society. We have dealt with this psychosomatic entity long hours of the day and night since the time when on entering school we first took scalpel in hand to dissect the structures of the human body. We have explored not only man's construction but have learned and are constantly learning more of his functions. There we have found laid down intricate patterns of reflex and hormonal interactions, eons old, and plainly related to adaptation to a world environment. Not less certainly have we observed in the varied and recurring crises in man's affairs in which our assistance is implored, the constancy of man's fundamental mental patterns, his fears, his aspirations, his instinctive devotions.

The physician knows not only that the essential mechanisms of man's body are unchanging except in terms of many thousands of years but also that man's essential beliefs in what he terms good and what he feels to be evil in human relations have a similar unchangeable quality. Built in to the warp and woof of the human mind and body by endless cycles of group living these beliefs are as permanent in their way as are the mechanisms of respiration.

The actions of man and the actions of nations are readily swayed toward good or bad ends, and mob psychology may even persuade the individuals of

a mob that what they do is good, and silence for a time the deeper individual knowledge that the action is evil. But mob hysteria is a tempest of wind that stirs the surface waters now this way and now that and man's own knowledge of what is good and evil is more akin to the eternal motion of the tides and the flow of the rivers to the sea.

There are causes of conflicts between nations in which the right and the wrong are far from clear. There are perhaps none in which there is not some right to both sides. In the present conflict, however, we have pledged ourselves to oppose a nation which has made it plain that it acts against some of man's deepest instincts of what is good in human relations. This nation has adopted faithlessness and treachery, intolerance and cruelty as a working code. It proclaims that its might gives it the right to subjugate weaker peoples. It proposes a world reorganized on such principles.

How far this hysterical crusade of the German people will carry them in the immediate future depends to a great extent upon the concerted efforts of our own nation. The quality of our effort depends in turn upon how deeply we feel the rightness of our cause.

We physicians, who know that such an outburst of national hysteria can have no more effect on the ultimate form of human society than a gale would have on the ebb and flow of the tides, must nevertheless as practical men recognize its destructive possibilities to our nation, to the people of our own generation and to their children. In this period in which all things are questioned we may from our knowledge and experience affirm the validity and the ageless character of man's perception of plain right and wrong in human affairs. We may each serve as a firm mooring post for those weak vessels that might otherwise drift with the wind.

M. C. PINCOFFS

REVIEWS

Night Nursing. By CATHERINE E. REILLY, R. N., Night Supervisor, Chester County Hospital, West Chester, Pa. 154 pages; 15 × 23 cm. F. A. Davis Company, Philadelphia. 1940. Price, \$2.00.

This book is one of the very few works on night nursing as a special field. It is attractively bound, and the subject matter is accurate and concise. The sound philosophy which runs through its pages is particularly appealing, and warrants its serious consideration not only as a collateral reading textbook for training schools, but also as a book to be read profitably by parents of those already in training and those considering entering a training school for nurses.

The technical suggestions are practical. Even an experienced clinician can gain much from the perusal of its pages, for it gives an intelligent insight into the problems which continually confront The Lady with the Flashlight.

H. P., Jr.

Handbook of Skin Diseases: A Practical Guide to Diagnosis and Treatment. By LEON H. WARREN. 321 pages; 13 × 19 cm. Paul B. Hoeber, Inc., New York, N. Y. 1940. Price, \$3.50.

"The Handbook of Skin Diseases" is unusual in a number of respects. It completely lacks illustrations and the descriptions of the morphology of lesions are minimal. The clinical and pathological features of skin lesions are outlined briefly and therapy is scantily discussed. For these reasons it is not recommended as a teaching text.

It contains, however, certain admirable features. The chapter on the "General Principles of Therapy" is very helpful. The alphabetical listing of the diseases is useful to the trained practitioner who desires a quick short reference to a special dermatosis. The interpretation of the etymology of the names of skin diseases is very interesting.

F. A. E.

The Neuroses in War. By several authors, edited by EMANUEL MILLER. 250 pages; 14 × 21 cm. The Macmillan Co., New York. 1940. Price, \$2.50.

This book, the product of British psychiatrists, most of whom had military experience during the last World War, is very timely and should prove to be of real value to medical men who are now interested in problems of military medicine. The authors show clearly why Selective Service authorities are anxious to keep out of the U. S. Army men who are psychoneurotic, psychopathic or emotionally unstable. Such men in active service do much to disrupt morale, and after service account for a large proportion of the expense of pensions.

The first chapter constitutes an excellent survey of the literature of neuroses in war. It covers the many official and non-official books and articles that came out of the last war, British, American, French and German.

The next four chapters describe the war time conditions under which neuroses occur, and the types most commonly seen at advance posts as well as in base hospitals. Two of the authors had opportunities to observe psychiatric cases in medical as well as surgical services. Two separate studies showed that 75 per cent of the cases on medical wards of base hospitals were primarily functional. Discussing "effort syndrome" as the commonest functional cardiac type, the authors state, "It will do irreparable harm to the effort syndrome patient if he is evacuated, under a cardiological label, to a general hospital; for, to quote the American Medical History of the 1914-18 war, 'the general hospital is the culture medium of the effort syndrome.'"

There are three chapters on treatment, stressing particularly methods applicable to conditions of active service. The authors point out the experience of nearly every one that functional cases seen and recognized early are relatively easy to treat and respond in a gratifying manner to prompt and vigorous psychotherapy. A large proportion of such cases, treated near the field of action, can be sent back to active service without being evacuated. However, the large number of functional cases that are not recognized, and are sent back to base hospitals, somehow become chronic and very resistant to any form of therapy.

The tone of the book is practical, the theories are conservative and sound, and the language is refreshingly free from the "jargon" of any school of thought. One chapter deals with psychiatric organization in the services. One chapter discusses the psychology of civilian morale and the "war of nerves." The book ends with a chapter written by H. Crichton-Miller, in which he summarizes the main findings and conclusions.

H. W. N.

Strange Malady; The Story of Allergy. By WARREN T. VAUGHN, M.D. 268 pages; 15 × 22 cm. Doubleday, Doran and Company, Inc., New York. 1941. Price, \$3.00.

The book is written in an interesting, nontechnical manner with the aid of cartoons to illustrate principles and theories of allergy.

It presents a very short history of medicine and a more detailed history of allergy and immunity. It deals with the many manifestations of allergy and much space is given to amusing and troublesome problems encountered. Mention is made of the great variety of allergens and some of the difficulties involved in their detection. Due consideration is given to emotional influences and conditioned reflexes in the initiation of symptoms in allergic disorders.

The general principles of treatment are given. The importance of the observance of fundamental rules is impressed on the reader by the review of alarming and also fatal accidents which have occurred on the basis of hypersensitivity. However, the book tends to develop an attitude of optimism toward the present state and the future of the study of allergy.

The book will be of interest and aid to the patient who has an allergic disease or to one who has a history of allergy in his family.

S. E. M.

Diseases of the Digestive System. By EUGENE ROSENTHAL, M.D., and R. J. V. PULVERTAFT, M.D. 394 pages; 18 × 25 cm. C. V. Mosby Co., St. Louis. 1940. Price, \$8.50.

The need for a comprehensive volume dealing with gastroenterology has been well met by "Diseases of the Digestive System." The authors have been able to assemble the fundamental information necessary for an understanding of the subject, without overburdening the reader with unessentials or references to controversial points. Although intended primarily for medical students, the book provides a reference work well adapted to the needs of the practitioner or even the specialist in the field.

By using numerous analytical diagrams and colored charts, the writers have evolved a system of teaching that is refreshing and quite valuable in effecting its purpose. Although Dr. Rosenthal writes from continental Europe, the point of view throughout his text is in harmony with the teachings of this country.

Here is a book that takes the straight path in a field in which the uninitiated can be easily misdirected. It is well recommended for supplementary reading in gastroenterology.

F. G. D.



ROGER I. LEE
PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS, 1941-1942

COLLEGE NEWS NOTES

THE BOSTON SESSION OF THE COLLEGE

The 25th Annual Session of the College, held in Boston, April 21-25, 1941, produced the largest gross attendance of any Meeting in the College history—although the New York Session in 1938 produced the largest member attendance. Physicians were present from forty-six states and the District of Columbia (Nevada and New Mexico were not represented), from Puerto Rico, from seven provinces of Canada, from Panama, China, Cuba, Mexico, and from Chile and Colombia of South America. The following is a comparative summary of the registration for the past four years:

		Members	Guest Physicians	Guest Non- Physicians	Students	Exhibitors	Ladies	Total
Boston	(1941)	1364	556	33	129	230	469	2781
Cleveland	(1940)	1221	710	25	116	223	262	2557
New Orleans	(1939)	896	525	16	499	167	578	2681
New York	(1938)	1447	463	24	3	291	319	2547

The gross attendance from the leading states was as follows:

Massachusetts	805	Ohio	103	Indiana	49
New York	408	Connecticut	87	Maryland	49
Pennsylvania	244	New Jersey	75	California	46
Michigan	111	Illinois	62	Rhode Island	46
		Canada	53		

It was observed that those states which hold regional meetings produced the largest percentage of member attendance.

The number in attendance frequently taxed the capacities of the ballroom and other meeting places. A new feature in entertainment was a concert by the Boston Symphony Orchestra under the direction of Dr. Serge Koussevitzky, complimentary to the College members. This nationally famous orchestra and its talented conductor gave a concert deeply appreciated, as evidenced by the attendance of more than 2500 physicians and their guests. A beautifully executed testimonial signed by the President and Secretary General was presented to Dr. Koussevitzky in appreciation of his concert and in recognition of his talents, the testimonial reading:

“AMERICAN COLLEGE OF PHYSICIANS

to

SERGE KOUSSEVITZKY

By thy art, thou callest forth concourses of sweet sounds to succor those whose life's aim is to comfort and to cure, and so do we, humble disciples of the healing art, acclaim thee as Master Healer of us all.”

The Convocation on Wednesday evening, April 23, was attended by a capacity audience. The Presidential Address by Dr. James D. Bruce and the Convocational Oration by Dr. James Alex. Miller, both dealing with the primary interests and activities of the College, were received with enthusiasm and will be published in this



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FIG. 1. Dr. Serge Koussevitzky, reading College testimonial.

journal. Fellowships were conferred upon 306* physicians who had qualified during the past year, and Dr. James Alex. Miller, the Convocation orator and former President of the College, received the only Mastership conferred this year. Masters of the College are those who have already attained the rank of Fellows and who, on account of personal character, positions of influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Credentials to the Board of Regents for special and well-earned distinction. Dr. Miller, in addition to having been one of the past Presidents of the College, is Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons; former President of the New York Academy of Medicine; a Diplomate of the American Board of Internal Medicine; Consulting Physician to the Trudeau Sanatorium, Presbyterian, Bellevue and Methodist Hospitals, and the New York Post-Graduate Medical School and Hospital. He has served the College many years in many important capacities, including Chairman of the Executive Committee; Chairman of the Finance Committee; Chairman of the Committee on Survey and Future Policy; and General Chairman of the New York Annual Session in 1938. During his Presidency the final draft of the application for the formation of the American Board of Internal Medicine was submitted to the Advisory Board of Medical Specialties, and it was through his initiative while President of the College that the original plans were executed for the acquisition of a permanent College home.

The Annual Banquet of the College on Thursday evening, April 24, was also attended by a capacity group. Dr. Earnest Albert Hooton, Professor of Anthropology at Harvard University, gave an amusing and thought-provoking address on "Hip-Hip-Hippocrates, or An Anthropological Cheer for Medicine." Dr. William B. Breed was Toastmaster and in his inimitable manner was, to say the least, a

* GEOGRAPHICAL DISTRIBUTION OF NEWLY-ELECTED FELLOWS, 1940-41

Alabama	3	Oregon	2
Arizona	1	Pennsylvania	32
Arkansas	1	Rhode Island	1
California	10	South Carolina	2
Colorado	5	Tennessee	4
Connecticut	7	Texas	10
Delaware	2	Utah	2
District of Columbia	6	Vermont	1
Florida	4	Virginia	5
Georgia	6	Washington	5
Idaho	1	West Virginia	4
Illinois	9	Wisconsin	1
Indiana	6	Wyoming	1
Iowa	1	Medical Corps, U. S. A.	10
Kansas	1	Medical Corps, U. S. N.	4
Kentucky	4	U. S. Public Health Service	3
Louisiana	7	Puerto Rico	4
Maine	1	Dominion of Canada:	
Maryland	2	Alberta	1
Massachusetts	13	British Columbia	1
Michigan	10	Ontario	1
Minnesota	6	Nova Scotia	1
Missouri	6	New Brunswick	1
Montana	1	Saskatchewan	1
Nebraska	3		6
Nevada	1	Brought Forward	292
New Hampshire	1	Bahamas	1
New Jersey	2	Cuba	12
New York	62	Turkey	1
North Carolina	5		
Ohio	6		
Oklahoma	2		306

"howling" success. The Surgeon General of the U. S. Army, Major General James C. Magee, was introduced and made a brief address, as did also the retiring President, Dr. James D. Bruce, Ann Arbor, the newly inducted President, Dr. Roger I. Lee, Boston, and the President-Elect, Dr. James E. Paullin, Atlanta.

The program of entertainment for visiting women was a most attractive one, with a local committee working at all times for the pleasure and comfort of the visiting wives and families. It had been estimated that there would be only three hundred guests to be entertained by the Ladies Committee, but there were actually four hundred and sixty-nine. Although the increased number made some strain upon the original budget and facilities, the local committee handled the entire program and arrangements most successfully and to the satisfaction of all.

Post-Meeting reports on the program all indicated a deep appreciation and high regard for the General Sessions, Morning Lectures, Panel Discussions and Clinics. The ballroom of the Hotel Statler frequently was filled beyond seating capacity for the General Sessions. The Panel Discussions were all well attended and many of the room capacities were exhausted. Especially favorable comments were heard concerning all of the Clinics, due particularly to the local committee arranging a program of real clinics where patients were shown.

THE 1941 ANNUAL BUSINESS MEETING

The General Business Meeting, held in conjunction with the 25th Annual Session of the American College of Physicians, convened in the Hotel Statler Ballroom, Thursday, April 24, 1941, at 5:30 p.m., with President Bruce presiding and Mr. E. R. Loveland acting as Secretary. The Secretary read abstracted minutes of the preceding Annual Business Meeting, which were approved as read.

Dr. William D. Stroud, Treasurer, presented the following report:

"Mr. President and Members: The finances of the American College of Physicians, as usual, are under the general supervision of its Board of Regents, and more especially supervised by the Committee on Finance. The accounts are recorded in the Executive Offices, according to accepted accounting principles, and audited by a certified public accountant.

"The 1940 operations of the College indicate a satisfactory financial situation. Through growth and life membership subscriptions and a transfer of \$25,000.00 by the Board of Regents from the General Fund to the Endowment Fund, the Endowment Fund, on December 3, 1940, amounted to \$126,346.22. The General Fund amounted to \$146,922.48. Therefore, the total assets (book value) of the College are \$273,268.70. The net increase in capital for both funds for the past year was \$27,315.51. Our investments have paid a little over 4 per cent. A full, detailed financial statement will be published in an early issue of the ANNALS OF INTERNAL MEDICINE for the information of all members.

"Upon recommendation of the Finance Committee and the subsequent approval of the Board of Regents, the Budget for 1941 has been adopted, calling for an estimated income of \$113,800.00 and an estimated expenditure of \$100,644.00. Respectfully submitted by William D. Stroud, Treasurer."

Mr. E. R. Loveland, Executive Secretary, presented the following report:

"The Executive Secretary's report is supplementary to the reports of the Treasurer and the Secretary-General. Much that has happened in the College, has also been covered in the annual address of the President.

"The past year again has been characterized by a definite increase in the activities of the College and in the duties of the Executive Offices, but at the same time our work has been rendered more interesting by its diversity and the coöperation and

kindly aid of the Officers, Regents and the Governors. The Secretary-General will give you a report on the College membership. I would like to pay tribute especially to the Committee on Credentials which makes a tremendous contribution to this College in time and in most careful work. When you hear the number of candidates elected, you should remember that the credentials of a much greater number have been submitted and reviewed. Credit should be distinctly given to all of the College Committees and to the College Boards. They are always present at our meetings and I have never in my experience known any group so interested and so attentive to their responsibilities. You have been fortunate in the selection of these men.

"During the past year your Editor has expanded the ANNALS OF INTERNAL MEDICINE by more than 300 pages over the preceding year. Much of the College literature, especially that referring to the requirements for admission, has been revised and republished. A supplement to the College Directory was issued and a new Directory, fully revised, will be published this coming summer. The long worked upon History of the College was completed and distributed this past year to the entire membership. At least a score of meetings have been conducted by the College Governors for their particular regions, as a result of which there has been an increased participation by our members in College affairs. These meetings contribute greatly to a better understanding of the objectives and activities of your organization. The Regents and the Governors individually have exhibited at all times a keen interest in and an effort to advance the College. The work of preparing for this Meeting, which bids fair to be one of the largest, if not the largest in the College history, has been lightened by the ready assistance and coöperation of President Bruce, General Chairman Breed and his efficient local committees. The registration to this time totals 2,781, of whom 469 are visiting women. While these are not all members of the College, the great majority are. We have studied the attendance records of several other national medical societies and we have found not one whose percentage of member attendance approaches the record of the College.

"We are gratified with the increasing number who have visited us at our Headquarters in Philadelphia, and we wish again to extend a most cordial welcome to our members and to express a desire to be of increasing service to them in the coming year. Respectfully submitted by E. R. Loveland, Executive Secretary."

Dr. George Morris Piersol, Secretary-General, presented the following report:

"*Membership*—Since the last Annual Session of the College we have lost by death 47 Fellows, 7 Associates, or a total of 54; by resignation, 2 Fellows, 3 Associates, total, 5; by failure to take up election, 1 Associate; by failure to qualify for advancement to Fellowship within the maximum five-year period prescribed by the By-Laws, 14 Associates; by delinquency, 4 Fellows and 1 Associate. Your attention is directed especially to the very small number of members who have failed to keep in good standing out of a membership so large as ours. The total membership mortality for the past year, therefore, has been 53 Fellows and 24 Associates; total, 77. There have been elected to Fellowship 306 physicians, only a few of whom were elected directly to Fellowship because of special qualifications and outstanding accomplishments. There have been elected to Associateship 273; 1 Fellow has been reinstated and 1 Fellow has been elevated to Mastership. The total membership of the College as now constituted is as follows:

4 Masters
3 371 Fellows
1,220 Associates
<hr/>
4,595 TOTAL
<hr/>

"Life Membership"—31 Fellows have become Life Members during the past year, making a grand total of 167, of whom 16 are deceased, leaving 151 on the roll at this time.

"One year ago a regulation was adopted providing that all candidates elected thereafter, when coming up for advancement to Fellowship, shall present satisfactory evidence of certification by their national board of certification where such a board exists, this rule, however, not applying to candidates from the Army, Navy and Public Health Service, nor to Associates elected prior to April 6, 1940.

"The Committee on Postgraduate Education, with the whole-hearted coöperation of the Governors and many of our Fellows, extended the program of intensive postgraduate courses this past year. Whereas for the year previous there were but five such courses given, this year there were eight, two of which were given during February and six of which were given just preceding the opening of this Session. The courses given were as follows:

Allergy at the Roosevelt Hospital, New York City;
 Gastrointestinal Diseases at the Mayo Foundation, Rochester;
 General Medicine at Harvard Medical School, Boston;
 Allergy at the Massachusetts General Hospital, Boston;
 Gastro-enterology at the Boston University School of Medicine;
 General Medicine at the University of Michigan Medical School, Ann Arbor;
 Clinical Medicine from the Hematologic Viewpoint at Ohio State University College of Medicine, Columbus;
 Cardiovascular Diseases at the University of Pennsylvania, Philadelphia.

The course in General Medicine at Harvard University was for a period of three weeks; the other courses were given for periods of one to two weeks.

"Three additional Research Fellowships have been voted by the College this year, these fellowships to go into effect on July 1, next."

The Secretary-General, Dr. Piersol, proceeded:

"And now, Dr. Bruce, during the past year, while you so ably and so wisely guarded the destinies of this College, you have become more than ever endeared to all of us, who have had the privilege of working with you. We are deeply appreciative of the never-failing spirit of coöperation and courtesy which you have shown in your work with the College.

"Therefore, on behalf of the Officers, Regents, Governors of the American College of Physicians, I have the honor to present to you this gavel as an enduring symbol of the high office you have occupied, as well as a token of our affection and esteem." (Applause)

PRESIDENT BRUCE: "Thank you very much; I am very deeply grateful to you. It seems scarcely possible that a year has passed since Dr. O. H. Perry Pepper at the Cleveland Session passed on to me the honor of the Presidency of this College. I was deeply impressed and grateful for the honor, but this was almost, if not quite, overshadowed by my sense of responsibility when I thought of those figures in American Medicine in whose footsteps I was about to follow.

"However, when I realized that all of our Officers and members stood ready at all times to meet requests for advice and assistance, I soon came to feel a greater sense of confidence. This is as it should be in a truly democratic organization such as ours, and so the year has passed happily for me, and uneventfully for the College.

"Although this country is now facing a decision, probably the most momentous in our own as well as in world history, it is related that when General Wolfe was with a small flotilla of boats and was slipping by the Fortress of Quebec seeking a landing,

he recited to his officers Gray's 'Elegy Written in a Country Churchyard.' In the silence which followed, he turned to his officers and said: 'Gentlemen, I would sooner be the author of this book than to take Quebec.'

"This is the way I feel about the honor you have bestowed upon me. I would rather have been your choice for President than the recipient of any other honor of which you or I can think.

"In completing my term of office as your President and returning to the ranks, it will be with an ever greater and increasing interest in the onward march of the College."

Dr. Roger I. Lee, President-Elect of the College, was then introduced by retiring President Bruce and inducted to office amid applause.

PRESIDENT LEE: "President Bruce—because he is still really President—Fellows of the American College of Physicians, I know the hour is late, but I would be less than human if I did not venture to express to you my thanks at the great honor which you have passed on to me. It is, I think, the greatest honor that could come to any man to be recognized as a leader for a year of his chosen profession and of his specialty within that profession, and to the College I promise the devotion of whatever talents I may have, and furthermore, under what leadership I may have, I promise the active, aggressive support of the College to those causes of freedom, democracy and safety of our whole continent of America." (Applause)

President Lee called for a report of the Committee on Nominations. In the absence of its Chairman, Dr. David P. Barr, the following report of the Committee was presented by Dr. Charles F. Tenney, Committee member:

"A—For the Elective Offices:

President-Elect James E. Paullin, Atlanta, Ga.
First Vice President D. Sclater Lewis, Montreal, Que.
Second Vice President Thomas T. Holt, Wichita, Kan.
Third Vice President Samuel E. Munson, Springfield, Ill.

(The list of nominees has been published in accordance with the directions of the By-Laws in the February Issue of the ANNALS OF INTERNAL MEDICINE.)

"B—For the Board of Regents:

Term Expiring 1944

Hugh J. Morgan, Nashville, Tenn.
 Ernest E. Irons, Chicago, Ill.
 T. Homer Coffen, Portland, Ore.
 Jonathan C. Meakins, Montreal, Que.
 James D. Bruce, Ann Arbor, Mich.

"C—For the Board of Governors:

Term Expiring 1942

Lawrence Parsons, Reno NEVADA *

Term Expiring 1943

Charles Henry Sprague, Boise IDAHO *

* New Territories that have now qualified to have Governors.

Term Expiring 1944

Roy E. Thomas, Los Angeles	CALIFORNIA (Southern)
James J. Waring, Denver	COLORADO
Charles H. Turkington, Litchfield	CONNECTICUT
Wallace M. Yater, Washington	DISTRICT OF COLUMBIA
Cecil McKee Jack, Decatur	ILLINOIS (Southern)
Robert M. Moore, Indianapolis	INDIANA
Harold H. Jones, Winfield	KANSAS
William B. Breed, Boston	MASSACHUSETTS
Warren Thompson, Omaha	NEBRASKA
Nelson G. Russell, Sr., Buffalo	NEW YORK (Western)
Leander A. Riely, Oklahoma City	OKLAHOMA
Edward L. Bortz, Philadelphia	PENNSYLVANIA (Eastern)
R. R. Snowden, Pittsburgh	PENNSYLVANIA (Western)
John L. Calene, Aberdeen	SOUTH DAKOTA
William C. Chaney, Memphis	TENNESSEE
Louis E. Viko, Salt Lake City	UTAH
Harry L. Arnold, Honolulu	HAWAII
Warren Soper Lyman, Ottawa	ONTARIO
Francisco de P. Miranda, Mexico City ..	MEXICO *
Lawrence Getz, Ancon	REPUBLIC OF PANAMA and the CANAL ZONE

Respectfully submitted,

REGINALD FITZ
 FRED M. SMITH
 CHARLES F. TENNEY
 ERNEST B. BRADLEY
 DAVID P. BARR, Chairman
 Committee on Nominations"

Each section was acted upon separately and President Lee in each instance asked for nominations from the floor, if there were any to be made. In due course and according to parliamentary rule, each nominee presented by the Committee on Nominations was officially elected to office. President Lee appointed a committee of two to conduct the President-Elect to the platform.

President-Elect Paullin made a brief address and pledged himself to the best of his ability to carry out the traditions of the College in the future.

President Lee then read a letter of appreciation from Dr. Serge Koussevitzky, Conductor of the Boston Symphony Orchestra, for the honor and the testimonial that had been issued to him by the College.

Dr. Wallace M. Yater presented the following resolution:

"BE IT RESOLVED: That the cordial and sincere thanks of the entire membership of the American College of Physicians be extended to our retiring President, Dr. James D. Bruce, to the General Chairman, Dr. William B. Breed, to the new President, Dr. Roger I. Lee, to the Chairman and members of the Boston Committees, individually and collectively, to Mrs. Donald S. King and her most courteous and efficient Committee on Ladies' Entertainment for their faithful and superior work in the conduct of this memorable Session, and

* New territories that have now qualified to have Governors.

"BE IT FURTHER RESOLVED: That our appreciation be extended, also, to those co-operating agencies and medical schools, the hospitals, the Public Press, the Boston Symphony Orchestra and its Conductor, Serge Koussevitzky, the Boston Convention Bureau, and the Management and Staff of the Hotel Statler and the Copley Plaza for their coöperation and help, all of which has contributed so much to our entertainment, pleasure and comfort."

The motion was duly seconded and there was a chorus of "ayes" for its unanimous adoption. President Lee asked the General Chairman, Dr. William B. Breed, to stand, whereupon he received the ovation of the entire audience.

Adjournment.

THE POST-CONVENTION TOUR TO PLYMOUTH AND CAPE COD

Following the close of the 25th Annual Session of the College at Boston, a Post-Convention Tour was conducted to Plymouth, Cape Cod, and the Pilgrim Shore. The following were members of the party: Dr. and Mrs. George E. Baker, Casper, Wyo.; Dr. and Mrs. Clarence C. Campman, West Middlesex, Pa.; Dr. Tomás G. Guardia, Panama, R. P.; Dr. and Mrs. Ernest D. Hitchcock, Great Falls, Mont.; Dr. and Mrs. Earl L. Mills, Wichita, Kan.; Dr. and Mrs. Samuel G. Plice, Chicago, Ill.; Dr. and Mrs. William S. Reveno, Detroit, Mich.; Dr. Vernon C. Rowland, Cleveland, Ohio; Dr. and Mrs. Albert A. Schultz, Fort Dodge, Iowa; Miss Dorothy Smith, Omaha, Nebr.; Dr. and Mrs. James C. Stewart, Topeka, Kan.; Dr. and Mrs. George F. Stoney, Erie, Pa.; Dr. and Mrs. Warren Thompson, Omaha, Nebr.; Master Tommy Thompson, Omaha, Nebr.; Dr. and Mrs. William A. Lange, Brooklyn, N. Y.; Dr. and Mrs. Robert M. Purdie, Houston, Tex.; Dr. and Mrs. Philip W. Morgan, Emporia, Kan.; Dr. Edwin B. Jarrett, Baltimore, Md.

The group left Boston immediately following the close of the Annual Session on Friday, April 25, and visited Plymouth, Pilgrim Hall, Burial Hill, Plymouth Rock; traversed Cape Cod both by the North and South Shores; Duxbury, John Alden House; Home of Daniel Webster; Old Oaken Bucket House; and Adams Mansion. Unfortunately, the weather was unfavorable for maximum enjoyment, but the tour was reported as a successful and enjoyable event.

THE BOSTON TECHNICAL EXHIBIT

There were seventy-two individual exhibitors occupying a total of eighty-six Exhibit Booths. An interesting and attractive guide to the exhibits and to the products on display was issued to every physician. While the Exhibit was distributed widely because of physical facilities, the individual exhibits were carefully planned and attractively set up. The Exhibit was restricted to the field of internal medicine and its allied specialties, and was acclaimed to be one of the most valuable and most interesting technical medical exhibits ever sponsored by the College or any other medical society. The reports of the exhibitors were almost unanimously enthusiastic, which indicates general appreciation and interest on the part of our attending physicians in relation to exhibits when they are presented on a high scale.

ELECTIONS TO MEMBERSHIP, BOSTON, APRIL 20, 1941

Fellows

Aballi y Arellano, Angel Arturo, Havana, Cuba
Acton, Conrad, Baltimore, Md. ([MC], U. S. Army)

Alexander, Harry Allison, Boulder, Colo.
Andes, Jerome Eli, Tucson, Ariz.
Antonetti, Alfredo, Havana, Cuba
Armstrong, Harry George, (MC), U. S. Army
Averbuck, Samuel Harris, New York, N. Y.

Badger, Theodore Learnard, Boston, Mass.
Bailey, Frederick Randolph, New York, N. Y.
Baker, George Erwin, Casper, Wyo.
Beatty, Gerald Aloysius, Wilmington, Del.
Beck, Frederick, Ithaca, N. Y.
Bell, Joseph Clark, Louisville, Ky.
Betha, James McRae, Memphis, Tenn.
Billings, Edward Gregory, Denver, Colo.
Bisbé y Alberni, José, Havana, Cuba
Blackford, Staige Davis, Charlottesville, Va.
Bond, George Samuel, Indianapolis, Ind.
Bower, Albert Gordon, Glendale, Calif.
Boyd, Douglas, Highland Park, Ill.
Brimmer, Karl Walter, Washington, D. C.
Brown, Daniel Noyes, New York, N. Y.
Bruenn, Howard Gerald, New York, N. Y.
Buie, Neil Dugald, Marlin, Tex.
Bullowa, Jesse Godfrey Moritz, New York, N. Y.
Burkhardt, Edward Arnold, New York, N. Y.
Burtness, Hildahl Ingbert, Santa Barbara, Calif.

Cantor, Maxwell Mordcai, Edmonton, Alta., Can.
Cardénas y Pupo, Carlos F., Havana, Cuba
Centurión, José J., Havana, Cuba
Chafee, Francis Hasseltine, Providence, R. I.
Chamberlain, Olin Burnham, Charleston, S. C.
Chesley, Faris Franklin, Chicago, Ill.
Cloyd, Augustus David, Omaha, Nebr.
Cole, Llewellyn Rathbun, Madison, Wis.
Connell, Walter Ford, Kingston, Ont., Can.
Cruikshank, John Merrill, Nassau, Bahamas
Curtis, John Kimberly, New York, N. Y.

Dameshek, William, Boston, Mass.
Daughton, Alva Duckett, Washington, D. C.
Davis, Aubrey Milton, Portland, Ore.
Dewey, Albert Warner, Gaziantep, Turkey
Dibble, John, (MC), U. S. Army
Dominguez, Cesar, Humacao, P. R.
Douglas, Albert Harris, Jamaica, L. I., N. Y.
Dozzi, Daniel Louis, Philadelphia, Pa.
Druet, Kenneth Lewis, Salina, Kan.
Dry, Thomas Jan, Rochester, Minn.
Duerfeldt, Treacy Henry, Tacoma, Wash.
Durham, Robert Brannan, Atlantic City, N. J.

Epstein, Harry H., Jamaica, L. I., N. Y.

Fariñas Mayo, Pedro Leandro, Havana, Cuba
Ferguson, Arthur Newton, Fort Wayne, Ind.
Ferree, John Willard, Indianapolis, Ind.
Findley, Thomas Palmer, Jr., St. Louis, Mo.
Finnegan, Francis Roman, St. Louis, Mo.
Friedberg, Charles Kaye, New York, N. Y.
Fulton, Marshall Nairne, Brookline, Mass.

Gay, Leslie Newton, Baltimore, Md.
Gillespie, James Ogilvie, (MC), U. S. Army
Golz, Harold Habich, Clarksburg, W. Va.
Green, Mack Macon, (MC), U. S. Army
Greenspan, Edward Bertram, New York, N. Y.
Gydesen, Carl Sophus, Colorado Springs, Colo.

Hamilton, Ian Bruce, Canton, Ohio
Hammonds, Everett England, Birmingham, Mich.
Harris, Robert Miller, Miami, Fla.
Herrell, Wallace Edgar, Rochester, Minn.
Hess, Charles Leonard, Bay City, Mich.
Hobson, Samuel, New Orleans, La.
Hogan, Bartholomew William, (MC), U. S. Navy
Holland, Harry Albert, Philadelphia, Pa.
Hollis, Ben Harvey, Louisville, Ky.
Holly, Leland E., Muskegon, Mich.
Hurst, Arthur Trimble, Louisville, Ky.
Hurtado, G., Felix, Havana, Cuba
Hussey, Hugh Hudson, Jr., Washington, D. C.
Hutton, John Evans, New York, N. Y.

Keeton, Robert Wood, Chicago, Ill.
Kelchner, Clyde Hartzell, Allentown, Pa.
Kelley, William Henry, Charleston, S. C.
Kendall, Charles Benjamin, (MC), U. S. Army
King, Frederick Herbert, New York, N. Y.
Kitchell, James Roderick, Philadelphia, Pa.
Knies, Phillip T., Columbus, Ohio
Kopecky, Leon Charles, San Antonio, Tex.

Labensky, Alfred, New London, Conn.
Landon Becerra, Jose, Santurce, San Juan, P. R.
Leiser, Rudolf, Eloise, Mich.
Lewis, Benton Oliver, U. S. Public Health Service
Lichtman, Solomon Sydney, New York, N. Y.
Lincoln, Miriam, Seattle, Wash.
Little, Joe Hollis, Mobile, Ala.
Livingston, Philip Henry, Chattanooga, Tenn.
Longfellow, Don, (MC), U. S. Army
Love, Julian, (MC), U. S. Navy
Lowance, Mason Ira, Atlanta, Ga.

Machle, Willard, Cincinnati, Ohio
Martin, Kirby Armstrong, New York, N. Y.

Mathers, Fred, Orlando, Fla.
McDaniel, Walter Shaw, Houston, Tex.
Mellen, Hyman Samuel, Detroit, Mich.
Meredith, William Cowan, New Rochelle, N. Y.
Metts, James Clayton, Savannah, Ga.
Mewborne, Edward Bruce, Newport News, Va.
Montoro Saladrigas, Octavio, Havana, Cuba
Moolten, Sylvan Elkan, New York, N. Y.
Moore, Ferrall Harmon, Palo Alto, Calif.
Muñiz, Jorge R., Havana, Cuba
Murphy, Alvin Edwin, St. George, S. I., N. Y.
Murphy, John Moylan, Detroit, Mich.

Nealon, Stephen William, Jr., Washington, D. C.
Nickum, John Stanley, Bridgeport, Conn.
Noyes, Edward A., (MC), U. S. Army

Ortega y Bolaño, Luis, Havana, Cuba
Ortiz y Ortiz, Antonio Maria, Santurce, San Juan, P. R.

Palmer, Harold Dean, Philadelphia, Pa.
Park, Felix Roman, Bala-Cynwyd, Pa.
Parker, Hubert McKibban, Kansas City, Mo.
Pawling, Jesse Randolph, Watertown, N. Y.
Petry, Howard Kistler, Harrisburg, Pa.
Poindexter, Samuel Marshall, Boise, Idaho

Quinn, David Edman, Livermore, Calif.

Reading, Robert Alvord, Cleveland, Ohio
Redmond, Arthur Douglas, Ogdensburg, N. Y.
Revercomb, Paul Houston, Charleston, W. Va.
Richison, Earl, (MC), U. S. Navy
Riggins, H. McLeod, New York, N. Y.
Rigney, Lawrence Joseph, Wilmington, Del.
Rosenak, Bernard David, Indianapolis, Ind.
Rudesill, Cecil Logan, Indianapolis, Ind.
Russell, Theodore Burg, New York, N. Y.

Scott, William Mastin, Shreveport, La.
Sebrell, William Henry, Jr., U. S. Public Health Service
Shahon, Henry Israel, New York, N. Y.
Shanno, Ralph Leopold, Forty Fort, Pa.
Short, Charles Lyman, Boston, Mass.
Silver, Solomon, New York, N. Y.
Simpson, Sutherland Eric, Watertown, N. Y.
Skinner, John Wylie, Kirkland, Wash.
Steele, Charles William, Lewiston, Maine
Stites, John, Louisville, Ky.
Sugg, Eugene Sifax, U. S. Public Health Service

Taylor, Fletcher Brandon, Oakland, Calif.
Taylor, Gurney, New York, N. Y.
Thomas, John Warrick, Cleveland, Ohio
Thompson, Ivan, Ogden, Utah
Thompson, Ralph Mathew, (MC), U. S. Army
Trapp, Carl Edward, Newton Centre, Mass.
Turrentine, Kilby Pairo, Kinston, N. C.
Tyson, Terence Lloyd, New York, N. Y.

Viamonte, J. Manuel, Havana, Cuba
Vieta y Barahona, Angel, Havana, Cuba

Walker, Helen Gertrude, Buffalo, N. Y.
Walker, William Clarence, Salt Lake City, Utah
Wanstrom, Ruth Cecelia, Ann Arbor, Mich.
Weilbaeher, Joseph Oswald, Jr., New Orleans, La.
Wilder, Gordon Botkin, Anderson, Ind.
Woldman, Edward Elbert, Cleveland, Ohio
Wulp, George Adolph, Hartford, Conn.

Zaur, Israel Sidney, Bridgeport, Conn.
Ziskind, Joseph, New Orleans, La.

Associates

Adlersberg, David, New York, N. Y.
Agnor, Elbert Boogher, Atlanta, Ga.
Arnett, Samuel Cullen, Jr., Lubbock, Tex.
Ashman, Leon, Baltimore, Md.
Atkinson, Arthur John, Chicago, Ill.

Bayley, William E. G., La Crosse, Wis.
Beckwith, Julian Ruffin, Charlottesville, Va.
Bell, Robert Alexander, (MC), U. S. Navy
Benson, Otis Otto, Jr., (MC), U. S. Army
Bradford, Aubrey Le Verne, (MC), U. S. Army
Brown, Robert Whitcomb, Fort Steilacoom, Wash.
Bruton, Martin Francis, Berwyn, Ill.
Burgeson, Paul Arthur, Warsaw, N. Y.
Burt, Kenneth Lewis, Howell, Mich.

Carroll, Hubert Henry, (MC), U. S. Navy
Chaikin, Nathan Wolf, New York, N. Y.
Childs, Edward Patterson, New York, N. Y.
Coggin, Charles Benjamin, Los Angeles, Calif.
Combs, Stuart Richardson, Terre Haute, Ind.
Cooper, Ralph Ruehle, Ann Arbor, Mich.
Cummings, Hatch Whitfield, Jr., Houston, Tex.

Dickey, Francis George, Baltimore, Md.
Downs, Charles McCabe, (MC), U. S. Army

Driscoll, Robert Edwin, Chicago, Ill.
Durham, J. Richard, Wilmington, Del.

Edwards, Robert Allison, Houston, Tex.
Eisele, C. Wesley, Chicago, Ill.
Ensworth, Herbert Kleber, New York, N. Y.
Evans, Earl Foster, (MC), U. S. Navy

Ferris, Lucian Minor, Vicksburg, Miss.
Fitts, Ralph Lamar, Grand Rapids, Mich.
Flickinger, Donald Davis, (MC), U. S. Army
Flynn, John Molloy, Boston, Mass.
Foulger, Margaret P. H., Philadelphia, Pa.

Gais, Elmer Stewart, New York, N. Y.
George, William Smith, (MC), U. S. Army
Goldberg, Samuel James, Jr., New Haven, Conn.
Gormley, Cyrus Martin, Butler, N. J.
Graham, William Donald, (MC), U. S. Army
Greaves, Frederick Clarence, (MC), U. S. Navy
Green, Mervin Edward, Ann Arbor, Mich.
Gross, Harry, New York, N. Y.
Grow, John Benson, (MC), U. S. Army
Gundersen, Svén Martin, Hanover, N. H.

Hale, Virginia Anne, Norwich, Conn.
Hays, James F., (MC), U. S. Navy
Healey, Claire Eliza, Ann Arbor, Mich.
Heavner, Lyle Everett, Detroit, Mich.
Hitzig, William Maxwell, New York, N. Y.
Holman, Charles Nixon, Portland, Ore.
Hopkins, B. Smith, Jr., Urbana, Ill.
Howell, Llewelyn Pennant, Rochester, Minn.
Hyman, Charles, Atlantic City, N. J.

Jaleski, Thomas Clarence, New Rochelle, N. Y.
Johnston, Alexander Henry, Glen Cove, N. Y.
Jordan, James Patrick, Buffalo, N. Y.

Katz, Sydney Milton, Brooklyn, N. Y.
Keeney, Edmund Ludlow, Baltimore, Md.
Kellogg, Frederick, Long Beach, Calif.
Kenamore, Bruce Delozier, St. Louis, Mo.
Kimbrough, Robert Cooke, Jr., Ann Arbor, Mich.
King, Boyd G., Cleveland, Ohio
Kirkpatrick, Charles Lee, (MC), U. S. Army
Klein, Andrew John Valois, East Orange, N. J.
Kroon, Harry C., Syracuse, N. Y.
Kubin, Milford T., (MC), U. S. Army
Kuraner, Heinz, (MC), U. S. Army
Kwitny, Isadore Jacob, Indianapolis, Ind.

Lang, Frederick R., (MC), U. S. Navy
Lynch, George William, Boston, Mass.
Lyons, Richard Hugh, Ann Arbor, Mich.

Maxwell, Richard Wesley, St. Louis, Mo.
McGinn, Sylvester, Boston, Mass.
Miller, Harry Dudley, Jr., Shelbyville, Ind.
Morgan, William Palmer, Austin, Tex.

Nolan, James Edward, Washington, D. C.
Norcross, John Wells, Boston, Mass.

Ogden, Ralph Trafton, Hartford, Conn.
Ogle, Dan Clark, (MC), U. S. Army
Osborne, John Randolph, Middletown, N. Y.
Owen, Kenneth Angle, Akron, Ohio

Pedden, John Rockwell, Grand Rapids, Mich.
Poole, Everett Blanks, Greenville, S. C.
Pritchett, Clark Poston, Columbus, Ohio
Pruitt, Francis Willard, (MC), U. S. Army

Query, Richard Zimri, Jr., Charlotte, N. C.

Rainey, John Faulkner, Anderson, S. C.
Rastetter, Joseph Walter, Milwaukee, Wis.
Rauschkolb, John Edward, Cleveland, Ohio
Ravid, Jacob Mordecai, Brooklyn, N. Y.
Reymont, Anthony Edward, Santa Fe, N. M.
Reynolds, Stephen, Ann Arbor, Mich.
Ricen, Edgar Moses, (MC), U. S. Navy
Richards, Richard Kohn, North Chicago, Ill.
Robishaw, Ruth Alice, Cleveland, Ohio
Rom, Jack, Detroit, Mich.
Rosenstiel, Henry Carl, Freeport, Ill.
Rosenthal, Phillip Jacob, Pittsburgh, Pa.

St. John, Clement Franklin, (MC), U. S. Army
Schneider, Ralph Frederick, New York, N. Y.
Schneiersen, S. Stanley, New York, N. Y.
Schwartz, William Spencer, Trudeau, N. Y.
Scott, Augustine Thornton, Lexington, Ky.
Segal, Maurice Sidney, Boston, Mass.
Senerchia, Fred Ferdinand, Jr., Elizabeth, N. J.
Serra, Lawrence Mario, Baltimore, Md.
Slater, Solomon R., Brooklyn, N. Y.
Smith, Henry Leon, Detroit, Mich.
Smith, Kenneth McLane, Ann Arbor, Mich.
Smith, Wilson Fitch, Hartford, Conn.
Souders, Carlton Remsberg, Boston, Mass.
Stannus, Donald George, Miami Beach, Fla.

Stefanic, Edward Joseph, Lakewood, Ohio
 Stefano, James Joseph, Brooklyn, N. Y.
 Steigmann, Frederick, Chicago, Ill.
 Stoneburner, Lewis T., III, Richmond, Va.
 Strauss, Arthur Simpson, White Plains, N. Y.
 Swindell, Orval Fisher, Boise, Idaho

Tempel, Carl Willard, (MC), U. S. Army
 Tocantins, Leandro Maues, Philadelphia, Pa.
 Top, Franklin Henry, Detroit, Mich.

Warr, Otis Sumter, Memphis, Tenn.
 Weingarten, Michael, New York, N. Y.
 Williams, Robert Jackson, Providence, R. I.
 Willis, Willard Harlan, Detroit, Mich.
 Winemiller, James Lewis, Great Neck, N. Y.
 Woods, Bertrand Odell, Portland, Ore.

Yeager, Robert Lee, Jr., Trudeau, N. Y.
 Young, Frank Walker, (MC), U. S. Army

AMERICAN COLLEGE OF PHYSICIANS TO MEET IN ST. PAUL, 1942

The Board of Regents announce that the Twenty-sixth Annual Session of the College will be held in St. Paul, Minn., April 20-24, inclusive, 1942, with general headquarters at the municipal auditorium. Hotel headquarters will be announced later.

The organization of the Session will be similar to that held in Boston, April, 1940, with hospital clinics and special lectures during the mornings, round table discussions around noon, and general sessions in the afternoons. The Convocation for the induction of new Fellows will be held on Wednesday evening and the Annual Banquet on Thursday evening.

The President, Dr. Roger I. Lee, 264 Beacon Street, Boston, Mass., will prepare the program of General Sessions and Morning Lectures. To him should be submitted applications for places on these programs.

Dr. John A. Lepak, 25 W. 4th Street, St. Paul, Minn., has been appointed General Chairman of the Session, and will have charge of the program of hospital clinics, round table discussions, entertainment and other local arrangements.

The general management of the Session, publication and distribution of programs, technical exhibits and related duties will be in charge of the Executive Secretary, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia, Pa.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Beaumont S. Cornell, Fort Wayne, Ind.
 Dr. Perk Lee Davis, Philadelphia, Pa.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

- Dr. Bernard I. Comroe, F.A.C.P., Philadelphia, Pa.—“Arthritis and Allied Conditions”;
 Dr. Harold J. Harris (Associate), Westport, N. Y.—“Brucellosis (Undulant Fever): Clinical and Subclinical.”

Reprints

- Dr. George M. Decherd, Jr., F.A.C.P., Galveston, Tex.—1 reprint;
 Dr. Charles F. De Garis, F.A.C.P., Oklahoma City, Okla.—3 reprints;
 Dr. Karl L. Dickens (Associate), New Orleans, La.—4 reprints;
 Dr. John N. Hayes, F.A.C.P., Saranac Lake, N. Y.—2 reprints;
 Dr. Oswald F. Hedley, F.A.C.P., Bethesda, Md.—1 reprint;
 Dr. Ben R. Heninger, F.A.C.P., New Orleans, La.—2 reprints;
 Dr. John L. Kantor, F.A.C.P., New York, N. Y.—4 reprints;
 Dr. Chester S. Keefer, F.A.C.P., Boston, Mass.—9 reprints;
 Dr. Jacob J. Kirshner (Associate), Philadelphia, Pa.—4 reprints;
 Dr. William B. Rawls, F.A.C.P., New York, N. Y.—2 reprints;
 Dr. Richard Kohn Richards (Associate), North Chicago, Ill.—5 reprints;
 Dr. Fred F. Senerchia, Jr. (Associate), Elizabeth, N. J.—1 reprint;
 Dr. Jacob Jesse Singer, F.A.C.P., Los Angeles, Calif.—3 reprints;
 Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn.—5 reprints;
 Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—1 reprint.

At the recent meeting of the Association of American Physicians Dr. James H. Means, F.A.C.P., Jackson Professor of Clinical Medicine at Harvard University Medical School and Chief of Medical Services at the Massachusetts General Hospital, was elected President of the Association. Among the other officers selected were: Dr. George Blumer, F.A.C.P., New Haven, Conn., Vice-President; Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., Secretary; Dr. Fred M. Smith, F.A.C.P., Iowa City, Iowa, Recorder; and Dr. William S. McCann, F.A.C.P., Rochester, N. Y., Treasurer.

Among the recent lecturers at the Woman's Medical College of Pennsylvania were: Dr. Sara M. Jordan, F.A.C.P., Boston, Mass., who spoke on “Peptic Ulcer”; and Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., who spoke on “The Art of Medicine.”

The first Annual Thomas McCrae Award of \$100.00 was granted to Dr. Robert F. Norris and Dr. Alexander Rush for the best publication in 1940 by younger members of the Medical Staff of the Pennsylvania Hospital, Philadelphia, Pa., at a special meeting, April 22, 1941.

Dr. Henry A. Christian, F.A.C.P., Hersey Professor of The Theory and Practice of Physic, Emeritus, Harvard University, addressed the audience on “Scholarship in Medicine.”

The Award, honoring Dr. McCrae, late Professor of Medicine at the Jefferson Medical College and late Chief of one of the medical services at the Pennsylvania Hospital, is to be granted annually to younger men of the Medical Staff for the best publication of work done primarily at the Pennsylvania Hospital.

Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill., was elected President of the Illinois Tuberculosis Association at the annual meeting held recently.

Among the speakers at a meeting of the Eleventh District Medical Association of Texas, April 24, 1941, were: Dr. Ralph Bowen, F.A.C.P., Houston, Tex., who spoke on "Gastro-intestinal and Respiratory Allergy in Children"; and Dr. Roy Turner, F.A.C.P., New Orleans, La., who spoke on "Shock in Medical Conditions, Physiology and Treatment."

Under the Presidency of Dr. Henry I. Klopp, F.A.C.P., Allentown, the Pennsylvania Psychiatric Society held its second regular Mid-Year Meeting, April 10, 1941, at the Allentown State Hospital.

On May 13, 1941, Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., gave a series of lectures on allergy at the University of Michigan Medical School, Ann Arbor in connection with the Annual Michigan Postgraduate Program for graduates in medicine. On May 14, 1941, Dr. Feinberg addressed the meeting of the Tenth Councilor District of the Indiana State Medical Association on "Nasal Allergy." On May 22, 1941, he spoke on "Allergy to Therapeutic Substances" before the Section on Medicine of the Illinois State Medical Society.

Dr. Harold J. Harris (Associate) has been commissioned Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., was reelected Speaker of the House of Delegates of the Medical Society of the State of New York at the annual meeting of the Society held at Buffalo, N. Y., April 29, 1941.

Dr. Chas. LeRoy Steinberg (Associate), Rochester, N. Y., gave a paper on "Dilute and Concentrated Preparations of the Tocopherols (Vitamin E) in the Treatment of Fibrositis" at the meeting of the Medical Society of the State of New York held at Buffalo, N. Y., April 29, 1941.

Recently, Dr. Steinberg was appointed a member of the Administrative Faculty of the School of Nursing to represent Medicine, at the Rochester General Hospital.

The Medical Society of New Jersey sponsored a Postgraduate Course in Pulmonary Tuberculosis at the Hudson County Tuberculosis Hospital, Jersey City, N. J.,

April 4-25, 1941. The course consisted of lectures, demonstrations, and round table discussions. Among those who conducted this course were:

Dr. Bernard S. Pollak, F.A.C.P.—Introduction to the Course;

Dr. Samuel Cohen (Associate)—"Clinical Classification of Pulmonary Tuberculosis";

Dr. Abraham E. Jaffin, F.A.C.P.—"The Rôle of the Physician and the Clinic (Demonstration of Tuberculin-Testing)";

Dr. Harry J. Perlberg, F.A.C.P.—"Interpretation of Fluoroscopic and X-Ray Findings in Pulmonary Tuberculosis."

The American Academy of Physical Medicine held its 19th Annual Meeting and Scientific Session in New York, N. Y., April 28-30, 1941. Among those who participated in the program of this meeting were:

Dr. Walter M. Solomon (Associate), Cleveland, Ohio—"Treatment of Fungus Infections by Iontophoresis";

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn.—"Methods of Applying Heat Locally in General Practice";

Dr. Irving Sherwood Wright, F.A.C.P., New York, N. Y.—"Physical Measures in Peripheral Vascular Disease";

Dr. Charles M. Griffith, F.A.C.P., and Dr. Hugo Mella, F.A.C.P., both of Washington, D. C.—"Disabilities Encountered Among Veterans of the World War."

Under the Presidency of Dr. Anthony Bassler, F.A.C.P., New York, N. Y., the National Gastroenterological Association held its 6th Annual Convention May 13-16, 1941, at New York, N. Y. Among those who participated in the program were:

Dr. Charles A. Doan, F.A.C.P., Dr. Phillip T. Knies, F.A.C.P., and Dr. Clark P. Pritchett (Associate), all of Columbus, Ohio—"Aluminum Hydroxide vs. Gelatin in the Treatment of Hypertrophic Gastritis";

Dr. Max Einhorn, F.A.C.P., and Dr. Henry A. Rafsky, F.A.C.P., both of New York, N. Y.—"Report of Two Cases of Probable Luetic Ulcers of the Stomach";

Dr. Henry A. Monat (Associate), Washington, D. C.—"Underweight: A Problem in Treatment";

Dr. Frank J. Gregg (Associate) and Dr. Roy R. Snowden, F.A.C.P., both of Pittsburgh, Pa.—"The Diagnosis of Functional Dyspepsia";

Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.—"Ulcerative Colitis and Its Management";

Dr. Louis H. Clerf, F.A.C.P., Philadelphia, Pa.—"The Importance of Gastroscopy in the Differential Diagnosis of Gastric Ulcer and Carcinoma";

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, Pa.—"The Rôle of the Gastrointestinal Tract in the Syndrome of Chronic Arthritis";

Dr. Lucius C. Sanders, F.A.C.P., Memphis, Tenn.—"Chronic Amebiasis."

Dr. Fred H. Voss, F.A.C.P., Kingston, N. Y., presided at a Round Table Conference on "A Consideration of the Newer Forms of Medical Therapy of Ulcers of the Stomach and Duodenum."

The 44th Annual Meeting of the American Gastro-enterological Association was held in Atlantic City, N. J., May 5-6, 1941, under the Presidency of Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill. Among the speakers at this meeting were:

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.—Presidential Address: "Some Recent Advances in the Physiology of the Alimentary Tract";

Dr. Russell S. Boles, F.A.C.P., Philadelphia, Pa.—"Qualitative Circulatory Deficiencies Observed in Peptic Ulcer: 1. The Chemical Composition of the Blood";

Dr. William A. Swalm, F.A.C.P., and Dr. Lester M. Morrison (Associate), both of Philadelphia, Pa.—"Pathologic and Gastrosopic Studies on the Incidence of Chronic Gastritis in Individuals with Gastric and Extra-Gastric Disease";

Dr. James B. Carey, F.A.C.P., and Dr. Ragnvald S. Ylvisaker, F.A.C.P., both of Minneapolis, Minn.—"Gastrosopic Observations in Achlorhydria";

Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.—"Nutrition Problems as Related to National Defense";

Dr. Abraham H. Aaron, F.A.C.P., and Dr. Frank Meyers (Associate), both of Buffalo, N. Y.—"Toxicity Studies on Stilbestrol";

Dr. Martin E. Rehfuess, F.A.C.P., Ardmore, Pa.—"Study of the Liver Bile as Obtained by Duodenal Intubation";

Dr. Charles A. Jones (Associate), Philadelphia, Pa.—"A Clinical and Laboratory Study of the Plasma in Obstructive Jaundice and Several Types of Non-Obstructive Jaundice";

Dr. John G. Mateer, F.A.C.P., and Dr. James I. Baltz (Associate); both of Detroit, Mich.—"A Comparative Evaluation of the Newer Liver Function Tests";

Dr. Seale Harris, F.A.C.P., and Dr. Seale Harris, Jr., F.A.C.P., both of Birmingham, Ala.—"The Genesis of Pellagra, Pernicious Anemia, and Sprue";

Dr. Rollin H. Moser, F.A.C.P., and Dr. Bernard D. Rosenak, F.A.C.P., both of Indianapolis, Ind.—"Gallbladder Dyspepsia";

Dr. Philip W. Brown, F.A.C.P., Rochester, Minn.—"The Prognosis of Regional Enteritis";

Dr. Albert F. R. Andresen, F.A.C.P., Brooklyn, N. Y.—"Ulcerative Colitis—An Allergic Phenomenon?";

Dr. Johannes Pessel, F.A.C.P., Trenton, N. J., and Dr. Jay M. Garner (Associate), Winnetka, Ill.—"Value of Color Stills and Cinematographic Records in Teaching Diseases of the Rectum and Sigmoid."

Dr. Russell S. Boles, F.A.C.P., Philadelphia, Pa., is First Vice-President of the Association; Dr. Sara M. Jordan, F.A.C.P., Boston, Mass., is Second Vice-President; Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y., is Treasurer; Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., is Recorder; and Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y., is Secretary.

The Graduate Fortnight of The New York Academy of Medicine will be held October 13-24, 1941. The subject this year is "Cardiovascular Diseases Including Hypertension." The Fortnight will present a carefully integrated program which will include panel discussions, clinics and clinical demonstrations, evening addresses, and a scientific exhibit. The evening sessions will be addressed by recognized authorities from leading medical centers of the United States and Canada. Among those who will participate in the program of evening lectures are:

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio—"Basic Hemodynamic Principles Essential to Interpretation of Cardiovascular Disorders";

Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Heart Failure";

Dr. Robert L. Levy, F.A.C.P., New York, N. Y.—"Diagnosis and Treatment of Coronary Insufficiency";

Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa.—"Observations on Social Significance and Recent Advances in the Treatment of Arteriosclerosis";

Dr. Emanuel Libman, F.A.C.P., New York, N.Y.—“Advances in Our Knowledge of Endocarditis—With Special Reference to the Therapy of Subacute Bacterial Endocarditis”;

Dr. Bernard S. Oppenheimer, F.A.C.P., New York, N. Y.—“Neurocirculatory Asthenia and Related Problems in Military Medicine”;

Dr. Edwin P. Maynard, Jr., F.A.C.P., Brooklyn, N. Y.—“Syphilis of the Cardiovascular System”;

Dr. Arthur C. DeGraff, F.A.C.P., New York, N. Y.—“Evaluation of Drugs Used in the Treatment of Cardiovascular Diseases”;

Dr. Irving S. Wright, F.A.C.P., New York, N. Y.—“Thrombophlebitis”;

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn.—“Thromboangiitis Obliterans”;

Dr. Harold E. B. Pardee, F.A.C.P., New York, N. Y.—“Management of Heart Disease in Pregnancy”;

Dr. Soma Weiss, F.A.C.P., Boston, Mass.—“Mechanism and Treatment of Pulmonary Edema.”

In connection with the “Clinical Day” presented by the Alumni Association of the University of Buffalo Medical School, April 5, 1941, at Buffalo, N. Y., Dr. Nelson G. Russell, F.A.C.P., Governor for Western New York, invited all members of the College, residing in this district, to be his guests for dinner.

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa., presented a paper on “Some Curable Types of Heart Disease” before the members of the Middlesex (N. J.) County Medical Society on March 19, 1941. On May 5, he addressed the 17th Annual Meeting of the American Association of the History of Medicine on “The Rôle of the Spanish Mission of California in Early American Medicine.” On May 12, Dr. Leaman was the guest speaker at the annual meeting of the West Virginia Heart Association held in Charleston, W. Va. The subject of his address was “Prognosis in Heart Disease.” On May 13, Dr. Leaman addressed the 74th Annual Meeting of the West Virginia Medical Association on “Recent Advances in Our Knowledge of Cardiovascular Disease with Special Reference to Their Clinical Application.”

Dr. Joseph C. Doane, F.A.C.P., Professor of Clinical Medicine, Temple University, has been appointed a member of the Board of Health of Philadelphia, Pennsylvania. The other members of the Board are Dr. Hubley R. Owen, Director of Public Health, and Dr. Arthur Parker Hitchens, Professor of Preventive Medicine, University of Pennsylvania.

NATIONAL DEFENSE POSITIONS FOR NURSES

The United States Civil Service Commission has announced a drive for nurses to fill important national defense positions. Two new Civil Service examinations in the nursing field are announced.

Announcement No. 88—Junior Graduate Nurse, \$1,620 a year; U. S. Public Health Service, Federal Security Agency; Veterans Administration; and Indian Field Service, Department of the Interior. Applicants will no longer be required to

take a written test, and the vision requirement has been modified. Applications will be rated as received until further public notice.

Announcement No. 85—Associate Public Health Nursing Consultant, \$3,200 a year; Assistant Public Health Nursing Consultant, \$2,600 a year; applications must be filed with the U. S. Civil Service Commission at Washington, D. C., not later than July 26, 1941. Examination is open only to registered graduate nurses who have completed a four-year College course, including, or supplemented by, at least one year of study in public health nursing, and have had experience in public health nursing supervision. Competitors will not be required to take a written test.

Full details of requirements may be obtained about any of the above appointments by communicating with the Civil Service Commission, Washington, D. C. Announcements from the Commission state that the need is urgent.

OBITUARIES

DR. JOHN J. MCGOVERN

Dr. John J. McGovern, a staunch supporter of organized medicine throughout all his professional life, passed away at his home, 2123 W. Highland Avenue, Milwaukee, on January 14, 1941. He had been ill for several years.

Dr. McGovern was born at Elkhart Lake, Wisconsin, February 14, 1864. Following his student days at the University of Wisconsin, he studied at Rush Medical College in Chicago, but was graduated from the University of Pennsylvania School of Medicine in Philadelphia in 1893. For the following two years, he was house physician at the University of Virginia Hospital. He then came back to Wisconsin and practised medicine in Milwaukee for almost fifty years, until his health became too poor to allow of further professional work.

He was a member of the staff at the Columbia Hospital and Johnston Emergency Hospital in Milwaukee. He was elected President of the Milwaukee County Medical Society in 1912. In 1928 he was made President of the State Medical Society of Wisconsin. He was also a member of the Milwaukee Academy of Medicine, Fellow of the American Medical Association, and became a Fellow in the American College of Physicians in 1927. He served one term as a member of the House of Delegates of the American Medical Association.

Dr. McGovern has given much of his time and energy for the progress of the medical profession. He was instrumental in securing the passage of the basic science law in Wisconsin and as a consequence, was given the Distinguished Service Award by the State Medical Society in 1931.

Surviving Dr. McGovern are his wife, Mrs. Grace Neilson McGovern, one brother, Francis E. McGovern, former Governor of the State of Wisconsin, and two daughters, three sons, and two grandchildren.

ELMER L. SEVRINGHAUS, M.D., F.A.C.P.,

Governor for Wisconsin

DR. HENRY KELLER MOHLER

Dr. Henry Keller Mohler, born 1887, died very suddenly on May 16, 1941, at his home, 480 N. Latches Lane, Merion, Pennsylvania.

Dr. Mohler received his M.D. from Jefferson Medical College of Philadelphia in 1912. He also held a degree of Ph.D. from the Philadelphia College of Pharmacy, and an honorary degree of D.Sc.

He was a renowned practitioner of Internal Medicine and Cardiology for many years. Since 1938, Dr. Mohler has been Dean of Jefferson Medi-

cal College of Philadelphia and also Sutherland M. Prevost Professor of Therapeutics.

Other positions which claimed his brilliant and scholarly mind were: Attending Physician and Physician in Charge of Sub-Department of Electrocardiology, Jefferson Hospital since 1938; Member of the Philadelphia Board of Health, and, for many years, Medical Director of Jefferson Hospital.

Dr. Mohler also claimed distinction as an author, being Associate Editor of "Cyclopedia of Medicine, Surgery and Specialties," and a contributor to Reimann's "Treatment in General Medicine." He was a Fellow of the American College of Physicians since 1923; also a member of the Philadelphia County Medical Society, the Pennsylvania State Medical Society, and a Fellow of the College of Physicians of Philadelphia and of the American Medical Association.

In the passing of Henry Mohler, Philadelphia Medicine has lost one of its outstanding members. He was deeply loved and respected by his colleagues, all of whom, together with a host of friends, accept with a sense of shock and grief, the untimely death of one so alive to the art and joy of living.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. WENDELL HEATH PAIGE

Dr. Wendell Heath Paige of Brownwood, Texas, died on February 14, 1941. He was born in Rutland, Vermont, on April 26, 1886, and received the degree of Doctor of Medicine from George Washington University in 1911. He served his internship at the George Washington University Hospital during 1911. During 1912 he served as Resident Physician at Starmont Sanitarium. Since 1926 he had been Internist and Director of Laboratory at the Medical Arts Hospital in Brownwood, of which organization he was one of the founders.

During the first World War Dr. Paige served in the Medical Corps of the United States Army, spending eleven months in France with the 144th Infantry, 36th Division, where he was awarded the Croix de Guerre for distinguished service. Since 1936 he had been Chairman of the Brown County Parole Board. He was a member of the Brown-Comanche-Mills-San Saba Counties Medical Society, the Fourth District Medical Society of Texas, of which he was president during 1938 and 1939, the State Medical Association of Texas, Texas Railway Surgeons Association, the American Heart Association, a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1938. In the death of Doctor Paige medicine has lost a staunch supporter of those principles for which the American College of Physicians stands, and he will be missed by all who knew him.

DR. STEWART RALPH ROBERTS

Dr. Stewart Ralph Roberts, aged 62, former member of the Board of Regents and former vice-president of the American College of Physicians, died April 15, 1941, at Atlanta, Georgia. He had been confined to his home only a few days, though he had never completely recovered from an illness which began in 1938.

Dr. Roberts was noted as a diagnostician and specialist in internal medicine and cardiology. During the World War he was chief of medical service of the Emory Unit Base Hospital No. 43, which he helped to organize. He was later transferred to Fort Jackson, Columbia, S. C., where as Lieutenant Colonel he was commanding officer of the base hospital. Dr. Roberts had unusual abilities as a lecturer and speaker. He was also a frequent contributor to medical journals. In 1912 he published "Pellagra," a definitive volume on the subject of this disease, in the preparation of which he made special studies at Harvard and in Europe.

Dr. Roberts received his degree of doctor of medicine from the Atlanta College of Physicians and Surgeons (later Emory University School of Medicine) in 1900, before reëntering Emory, to receive his A.B. degree in 1902. He was graduated with first honors. From the University of Chicago he received his degrees of bachelor of science and master of science. He then returned to teach biology, zoölogy, and physiology. After three years he moved to Atlanta, where he began to practice medicine with conspicuous success. He also taught in the medical school, which in 1915 became a part of Emory University. Since that time he has been professor of clinical medicine at Emory University.

Dr. Roberts had been president of the American Heart Association, the Southern Medical Association and the Fulton County Medical Society. He was a founder of the Emory Chapter of Phi Beta Kappa, and was a member of the Kappa Alpha Fraternity and various medical and honor societies.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,

Governor for Georgia

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